Note: The language on this website comes directly from the transcribed testimony taken at this panel meeting. The views and opinions are those of each of the experts and not those of the Centers for Medicare & Medicaid Services. CMS does not edit these transcripts and makes no assertion as to their accuracy.

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C O N T E N T S

P R O C E E D I N G S

Opening Remarks

MS. LAPPALAINEN: I would like to say good morning and welcome, Panel Chairperson and Committee Members and members of the audience. I am Sharon Lappalainen. I am the Executive Secretary of the Executive Committee of the Medicare Coverage Advisory Committee.

The committee is here today to hear reports from recent meetings of the Medicare Coverage Advisory Committee Medical Specialty Panels. The committee will also consider how to provide guidance to and substantive coordination among MCAC panels. For example, the committee will consider levels of evidence, types of information needed and the nature of issues that will be considered by the Medical Specialty Panels at future meetings.

For today's panel, I would also like to welcome Dr. Hugh Hill, who is with the Coverage and Analysis Group. Dr. Hill comes to us from the Johns Hopkins University. In addition to his duties, he will also serve as the HCFA liaison to the Executive Committee.

I would also like to read the conflict of interest statement to the record. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. The agency has determined that all members and consultants may participate in the matters before the committee today.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products or services they may wish to comment upon.

At this time, I would like to turn the meeting briefly over to our distinguished Chairperson, Dr. Sox, who will ask the members to introduce themselves.

DR. SOX: Thank you. Good morning. I think we will make introductions perhaps starting with Linda Bergthold. Could you say who you are, where you work and your role on the panel, please.

DR. BERGTHOLD: Sure. My name is Linda Bergthold. I am the consumer representative to the Executive Committee. I am from California.

MS. RICHNER: I am Randel Richner. I am the industry representative from Boston Scientific.

DR. FRANCIS: I am Leslie Francis. I am a professor of law and professor of philosophy at the University of Utah in Salt Lake City.

DR. HOLOHAN: I am Dr. Tom Holohan. I am trained in hematology, oncology. I am Chief of Patient Care Services for the Veterans Health Administration in the Washington, D.C. Headquarters.

DR. FERGUSON: John Ferguson. I am a neurologist and former Director of the National Institutes of Health Consensus Development Program for the last eleven years and now a public health consultant.

DR. MURRAY: I am Bob Murray. I am an attorney and biochemist at Lutheran General Hospital in Chicago, Vice Chairman of the Laboratory and Diagnostics Panel.

DR. BROOK: Hi. Robert Brook at RAND and UCLA.

DR. SOX: I am Hal Sox. I am a general internist. I chair the Department of Medicine at Dartmouth Medical School. I chair one of the panels and I guess I am also the Chair of the Executive Committee.

DR. HILL: I am Hugh Hill and I have been introduced.

DR. GARBER: I am Alan Garber. I am a professor of medicine at Stanford and staff physician at the Department of Veterans Affairs. I am Chair of the Medical and Surgical Procedures Panel.

DR. MAVES: I am Mike Maves. I am an otolaryngologist at Georgetown. I am President and CEO of the Consumer Health Care Products Association and I am the Vice Chair of the Medical and Surgical Panel.

DR. ALFORD-SMITH: I am Daisy Alford-Smith, Director of the Summit County Department of Human Services in Ohio, as well as the County Coordinator for all of its social services. I chair the DME Committee.

DR. JOHNSON: Joe Johnson, private practice, chiropractor. I am co-chair of the DME Committee.

Panel Business

MS. LAPPALAINEN: We have two items on the agenda for panel members. The first is to disclose the panel of the schedule of the Medicare Coverage Advisory Committee. That tentative schedule is available to you, the audience, as a handout. You can pick that up.

But I would like to remind the Executive Committee that their schedule is March 1st and 2nd, June 6th and 7th, and November 7th and 8th. I would like to note that these are tentative dates and that they could be subject to change.

The second item is the types of information that may come before MCAC, and I will defer to Dr. Hill,

who will make a few remarks on this item.

Also, I have been reminded by our audiovisual, that the small gooseneck microphones are extremely sensitive, and they will pick up your voice, so you don't need to bring them too close.

DR. HILL: Thank you, Sharon, I will be brief especially since I am within striking distance of Dr. Sox's gavel.

I am just going to review a couple of things from the charter and from the Federal Register notice about the panels and about the Executive Committee, and finish with one additional thought about what we are considering as appropriate for referral to panels.

The charter calls upon the committees to review and evaluate medical literature, to review technical assessments, to examine data and information on the effectiveness and appropriateness of medical services and items.

The panels are to develop technical advice to be reviewed and ratified by the MCAC, and the Executive Committee is to do three things: provide guidance to panels, facilitate substantive coordination among panels, and review and ratify panel reports and submit the report to HCFA.

Our Federal Register notice regarding our national coverage decisionmaking process provided that a referral to an MCAC or an outside assessment will involve issues that generally are complex and controversial, often involve broad health policy concerns.

The issues may require extensive consultation with specialty societies, medical researchers, and others familiar. In general, we may refer an issue to the MCAC if it's a subject of significant scientific or medical controversy, there is a major split in opinion among researchers and clinicians regarding the medical effectiveness of the service, the appropriateness of staff or setting, or some other significant controversy that would affect whether the service is "reasonable" and "necessary" under the Act.

Two. It has the potential to have a major impact on the Medicare program, and we define that broadly.

Three. It is subject to broad public controversy.

Finally, in addition to those criteria, we are internally talking about the propriety of referring to panels, issues that are close calls. When the medical literature and the scientific evidence are clear one way or the other that something is or is not reasonable and necessary, it may be easier for us to go ahead and decide that internally without referral to a panel.

Thank you.

DR. SOX: I would like to call upon Ron Milhorn, who is a health insurance specialist.

Mr. Milhorn.

HCFA Presentation - Levels of Evidence

Ron Milhorn

MR. MILHORN: Good morning.

[Slide.]

I want to briefly go over Medicare's use of medical evidence.

[Slide.]

Since its inception in '66, Medicare has used medical evidence to make its coverage decisions. In the early days, primarily due to necessity, relied to a great degree upon the informed opinion of consultants and professional societies, and those sorts of things.

Gradually, we developed a more evidence-based decisionmaking process.

[Slide.]

Over the past decade, we have increasingly stressed the need for published scientific studies in order to develop our coverage policies.

Our coverage notice, which we published on April 27th of this year, makes it clear that requesters, those who wish to investigate an issue for coverage, need to provide for us the published scientific evidence and, in some cases, unpublished scientific evidence, that is sufficient for us to review the issue and develop a covered policy whether yea or nay.

[Slide.]

Our general requirements--and I think I should point out at this juncture that we are currently working on a regulation or a proposed regulation actually that is supposed to outline the criteria to be used in making coverage decisions under Medicare--the primary purpose of this regulation is not to be the final word, but actually to provide an underpinning or a foundation for what we have called sector-specific guidance documents which will be much more narrowly focused toward drugs, devices, diagnostic imaging services, and that sort of thing.

We have, as some of you well know, made several attempts to publish a coverage regulation, 13 or 14,

in the history of the program, four in the last 10 years. None of them have been successful, at least in part because there is this tendency to say, ah, that paragraph doesn't apply to me, that sentence I don't like, and you get nibbled at that by ducks.

One of the ways we hope to avoid that, and we think we can avoid it, and also in the process provide useful information to those who want to come here and get something covered, is to be very much more specific as to the particular area of medical care that we are looking at.

In addition to the general requirement, though, that we use, and we are going to continue to use unless we get or until we get--I should say "until," not "unless"--we get this coverage regulation published in final and the guidance documents prepared, is that the service in question must demonstrate by authoritative evidence that it's medically effective. That's it. That's all there is to it, but it is, of course, a great deal more complicated than that.

In addition, our program has requirements as to the appropriateness of the service, and I will go to that in just a second.

[Slide.]

Authoritative evidence is written medical or scientific results demonstrating the medical effectiveness of the service. Generally, what we are looking for here is reports of such things as controlled clinical trials and peer-reviewed literature, and so on, and so forth, and there is, of course, a vast body of articles and books and papers as to what constitutes sufficient evidence.

We are searching for evidence that demonstrates the safety, the clinical effectiveness, and the comparative benefit if there are other services to which the service in question can be compared, compared to benefit of the service.

[Slide.]

Demonstrated effectiveness. What we are looking for here is three or four things. We sometimes don't get all of them. It depends upon the service in question and, to some degree, its level of development.

We are looking, first of all, for a positive evaluation of the benefits versus the risks, and this is done on a service-by-service basis. As I mentioned before, we have to prepare or we think we should prepare in order to make ourselves a little bit more clear sector-specific guidance documents.

One of the things that is the case here is that the sector-specific guidance documents themselves will outline the degree to which you need X number of people or approximately X number of people to power the study, and so on, and so forth.

So, we always get asked the question how much evidence do you need. The short answer--and we are

not being flippant--is enough, and enough tends to vary with the service in question.

We are looking also for improved health outcomes, either generally for a broad spectrum of patients or perhaps for a particular group of patients. If a service, for example, provides a substantial benefit for a very narrow range of patients, that is easy.

If it provides a less substantial benefit or perhaps no discernible benefit for a broader group of patients, one of the things we can and do do is narrow our coverage to account for those patients for whom the service has proven medical effectiveness.

As time goes by and as the service matures or is tested and refined, we may, and we often do, broaden that coverage to include additional groups of patients for whom the medical effectiveness has been demonstrated.

Finally, if applicable, FDA has determined the service is safe and efficacious. FDA's determination is one step, but by no means the only step, as those of you involved in devices well know, in getting Medicare coverage.

FDA looks primarily at does it work. The result, of course, is that to the degree that FDA has done a premarket approval as opposed to a 510(k), there is evidence of the efficacy of the service.

However, as one of our medical directors always used to say, "so what," what does it do for a patient or a particular group of patients, and that, although FDA sometimes gets into that area, that becomes then our bailiwick and the thing that we look at most carefully in many cases.

[Slide.]

Medically appropriate. We are not approving services as FDA does for marketing. We are trying to integrate these services into an existing program. Several things are very important for the Medicare program, and one of these is appropriateness of the service.

First of all, the patient has to have a suitable indication for the service. This may sound rather A, B, C, kindergarteny, but believe me, you would be amazed at some of the claims that come in.

The service is suitable for, but not in excess of, the patient's needs. In those cases where the service is in excess of the patient's needs, the classic one-hour office visit where a 15-minute visit would have been more than sufficient, we can and do refuse to cover the additional amount.

The term used in claims processing for this is downcoding, recoding the claim to a lesser service.

The service is furnished by qualified personnel. We have, in both our statute and in our regulations, long, long descriptions of who these personnel are and what they are authorized to do either by statute or

by regulations.

Finally, the service is furnished in a setting that is suitable for, but not in excess of, the patient's needs. Here again, this is a service-by-service question. Of course, we have services, for example, that are only reasonably furnished in hospitals. Others may be furnished in either hospitals or ambulatory surgical or outpatient surgical centers of one sort or another, and, of course, a good many of them in physician's offices.

[Slide.]

Appropriate evidence. Not all types of evidence are appropriate for all services. The so-called gold standard of randomized controlled clinical trials obviously are not going to be done on, for example, liver transplant patients, certainly not a blind or a double-blind study on surgical patients.

This sounds again rather kindergarteny, but we do get into big fights with people about this. Most people understand that, but it is worth repeating, that the amount and kind of evidence required is going to vary due to a number of factors, the nature of the service itself, whether there are alternatives available or not.

To be very blunt about it, if we have got a condition for which there is absolutely no alternative, the amount and kind of evidence is not quite as, shall we say, stiff or serious as the amount and kind of evidence for a service for a condition for which there is more than ample alternatives that apply to every patient who has that condition or illness.

The patient population likely to require the service. In some cases, the patients, of course, are obviously in very bad shape to begin with, and the kinds of rigorous trials that might be appropriate for other patients, may not be appropriate for them, and alternatives are found to be acceptable.

[Slide.]

Here is where we get into the real cat fights. Of course, again, what kind of evidence are you looking for? As I mentioned before, we are going to try and do this on a sector-specific basis because we are constantly arm wrestling about is this the right kind of evidence or enough.

In general--and I don't think we are too far off the reservation here--we have in the past ranked the kinds of evidence that are available in terms of the most authoritative to the least authoritative, and in doing this, I think it is worth emphasizing this several times.

This is not something that HCFA made up or the government made up. Ever since the program began, we have basically looked to the medical and scientific profession and asked them, okay, how do you decide these questions, how do you make up your mind about these kinds of things, and we have followed that pretty much over the past 33 and a half years.

The most authoritative, everyone I think agrees, maybe not, at least where it is appropriate, is the controlled clinical trial. The controlled clinical trial that has been published or at least accepted for publication or a condition for publication in a peer-reviewed journal.

There are various types of controlled clinical trials. Essentially, they all have the same feature, which is there is some sort of control, some sort of group that got standard medical treatment or did not get the treatment being tested.

All kinds of variations and flavors on this - blind, double-blind, and so forth, often depending upon the type of service being studied. A number of variables can affect the persuasiveness of these kinds of studies, the number and type of patient studied.

You will see controlled clinical trials with 20 patients, not as impressive as one with 200 patients generally. The statistical methodology that is used to come up with the results of the trial, the level of noncompliance, the dropout rates.

We have seen particularly in some surgeries crossover rates, as they are called, people in the control arm are allowed to cross over to the treatment arm, sometimes within three to six months, and so the long-term effect of the surgical procedure is pretty much lost in that kind of a trial.

You know how they were doing for six months, but after that, the control group or at least numbers and members of the control group, have in effect dropped out of the control group and moved over to the other arm.

[Slide.]

I have not gotten very original with my titles here. The next six slides you are going to see have the same title.

The age and health of the patients involved in the trial. We see a lot of trials, for example, where the cutoff age is 50 years old, and for the most part, it is another 15 years before you are entitled to Medicare unless you become disabled.

The inclusion and exclusion criteria where people are allowed in the trials that have multiple problems, others are restricted to people who only have the condition which is being treated.

This is highly important for the Medicare program because obviously, most of our patients have multiple problems. Believe me, I am 58 and I have already got multiple problems. I hate to think of what I am going to have when I am 65.

Internal inconsistencies. Dr. Holohan's famous diminishing denominator, we see it, unfortunately, even in peer-reviewed published studies where they start out with 287 patients, on page 2 there are 282, by

the time they get to page 5 there are 266 with no explanation of what happened to these people in the interim.

These are the kinds of things you will see, and they are the kinds of things that raise your eyebrows and you say, hmm, how much weight do I give this controlled clinical trial.

[Slide.]

Another area of evidence are the assessments that we contract with, primarily with the Agency for Health Care Policy and Research, although we do contract with private organizations, as well, either through them or directly.

An assessment is usually quite extensive, but it may be rather limited. It is used when the amount and kind of evidence is either extensive, or in some cases limited, and there are modeling or other techniques used to try and get to some conclusion, or where the evidence is in serious dispute, either as to what it demonstrates or as to whether the studies involved were properly done or properly reported.

Assessments represent an informed third party review, an evaluation of the available evidence. They are useful to us both with respect to the fact that we are able to tap into expertise we don't have here, as well as one step removed. This is not HCFA making this evaluation, this is a neutral third party who has no interest really in the outcome giving us an evaluation.

[Slide.]

Evaluations or studies initiated by Medicare contractors. We have a number of very talented folks around the country who are facing the three and a half million claims a day that this program generates, and in the process of doing so, they are required to make, not only the daily decisions as to the claim, but also to develop what they call local medical review policies, which often involve things which are very akin to the kinds of national coverage policies with which we deal.

In performing this function, they may do it alone in their particular area, they may do it together in groups, and we have a number of work groups formed of our contractor medical directors who give us very valuable advice, not only with respect to the medical and scientific evidence available, but also where the rubber meets the road in terms of how the claims processing system handles these things.

[Slide.]

Further down the list, reports on case studies that are published or accepted for publication. What we are looking for here are limited types of case studies that present treatment protocols, and these vary in terms of how comparative they are, and quite frankly, they are sort of at the bottom of the food chain in terms of medical evidence. They vary in terms of their worth in terms of making a coverage decision - case controlled studies, comparisons of a series of case histories usually, a cohort study, treatment versus

no treatment comparison.

There are a little different names for these, by the way. I was reading Dr. Garber's paper, and he at one point just gave up and said, under a variety of names that are under study.

[Slide.]

What we are looking for is slides that present treatment and perhaps patient selection protocols based on the evidence developed in the study, protocols as to who would and would not benefit from this treatment, and perhaps most importantly, whether the treatment is a late or last resort, or whether it should be moved quickly into standard treatment.

[Slide.]

Studies with very small numbers. Even if they are controlled clinical trials, we have seen controlled clinical trials, honest to God, with as few as 18 people in them. Whether they are done prospectively or retrospectively, individual case reports are generally not considered good evidence by most folks.

In summary, all evidence is not "equal" even amongst clinical trials. There are good ones, there are not so good ones, and then there are a lot in the middle, and so consequently, the fact that there is a--you know, we have got 20 clinical trials, what is enough?

One good clinical trial can be enough, 200 bad clinical trials can be less than we need. It all depends.

[Slide.]

Now we get to the fact that we have got these things, how do we look at them? We asked several questions. Obviously, as I mentioned, was the study published.

The posters at the conferences, we get those a lot. They are interesting, they are informative, but good medical evidence, not really.

What issues does the study present evidence for - is it looking at the clinical effectiveness of this treatment? Is it trying to determine what good patient selection is, its appropriate use, whether it's a late resort, a last resort, and so on, and so forth? How strong was the study, how big was it?

What was the study design? Was it a multi-center study or was it done only in one place? How was it implemented, how was the analysis done, and was the analysis sufficient, and does it hold up against the actual data that was produced by the study.

[Slide.]

How did the study relate to other studies? Usually, at least you would hope that if four or five people do controlled clinical trials in different places, their results will be very similar. Unfortunately, that is not always the case.

There are sometimes conflicts, and one of the things that you often look for here is, okay, why did those conflicts happen, are there some special factors that are not apparent from the study itself? Are there certain confluences that make sense, are there certain conflicts that don't appear to make sense? In short, you know you have to do some more digging.

Finally, is the evidence sufficient to reopen a coverage decision. One of the cautions, we usually, of course, only look at things that we have not covered in the past to see if they are covered from this point on.

But under our new process--and we actually have a live case here--when we make a coverage decision, anyone with an e-mail address or an envelope and a stamp can challenge that and say, hey, I don't think you made the right decision, I don't think you assessed the evidence properly, and so on, and so forth, and we reopen it and we look at it again. Again, good clinical trials can often change our minds rather substantially.

The thing you have to keep in mind is it may change our mind in the direction that perhaps the person who furnished it to us didn't want us to go.

[Slide.]

Just a word on medical versus clinical effectiveness. One of the things that we have to look at is whether the information that is presented to us--and this is extremely difficult to do, and quite frankly, I am not going to tell you we do it very well because sometimes we don't, but we do try--is whether this service is really what we would like to say ready for prime time.

It has been demonstrated to be effective in major medical centers where everybody is watching everybody else, and you have got the very best surgeons and the very best radiologists and the very best nurses, and so on, and so forth.

One of the reasons that when we cover transplants, we are very, very careful about the facilities in which we cover them, was there was obvious evidence that if you didn't have a facility that did it a certain way on certain patients, your success rate wasn't nearly as good as it should have been.

A service may be medically effective under strict protocols. It may be medically effective when done by very talented people in major medical centers. When it diffuses out to the community, it may lose some of that effectiveness - not always and usually not, but it can happen.

So, one of the things that you look for is not only the medical effectiveness as shown by the study, but try and predict the future a little bit to the general clinical effectiveness - how is this going to work when it gets out to the average hospital, the average doctor, the average nursing staff, and so on, and so forth.

To some degree, it usually doesn't matter. The availability of the service may override any diminution in the success of the service, particularly if you are looking at an area where there is no alternative, but in some cases, it can cause us to limit the coverage of the service to people who have had certain training, to facilities that have certain ancillary services. In short, we may not let this particular service just flow out there, but have some rules or some fences we put around it.

[Slide.]

I have pretty much gone through that, haven't I. These are often called appropriateness decisions as has been mentioned before.

[Slide.]

Cautionary tales, a few things to keep in mind. As I mentioned before, these rules are not our invention. They are our read on what the medical and scientific profession itself has come up with, and I think that is a very important point to keep stressing, because I have spent a lot of time at meetings where people are screaming at me across the table saying, hey, where did you come up with that. The honest answer is I didn't; the medical and scientific profession did.

Secondly, no coverage is static, believe me. Nothing ever gets settled around here. There is no final answer. The simple fact of the matter is that as new evidence is developed, as new techniques are developed as people develop ways of doing things that didn't work 10 or 15 years ago.

Coverage may come into existence down the road, it may be limited, it may expand, whatever.

Timing is important. I think if you paid any attention to our notice in April, it is obvious that when you come in here to make a formal request, you should have sufficient evidence for us to make a decision.

If you don't, the default position is no. If you are looking at evidence, and there isn't evidence or there isn't sufficient evidence, the no answer is the one that you would naturally gravitate to.

Assessing evidence is critical, it is complex, and believe me, there is three ways you can start a real fight - discuss religion, politics, or medical evidence. At least in this context, that certainly is true.

Any questions?

DR. SOX: I just want to give an opportunity to Executive Committee members who arrived late to introduce themselves - Dr. Eddy and Dr. Davis.

Dr. Eddy, tell us where you are from, what you do, and what your status is on the committee.

DR. EDDY: I apologize for being late, a little difficulty in finding the building, believe it or not.

I am an independent researcher and writer and speaker, and so forth. I am also a senior adviser to Kaiser Permanente, Southern California. My interests are in technology assessment and coverage decisions, and a variety of things. Other experience I have that might be pertinent to this committee is that I am a chief scientist for the Blue Cross/Blue Shield Association's tech program, which does its technology assessments. I am the Chair of the Diagnostic Imaging Committee or Panel, I believe.

DR. SOX: Thank you. And Dr. Davis.

DR. DAVIS: Thank you, Dr. Sox. I am sorry for being late, too. I just caught the red eye from San Diego, so if I look a little bleary-eyed, I apologize.

I am Ron Davis I am the Director of the center for Health Promotion and Disease Prevention at the Henry Ford Health System in Detroit. I am a preventive medicine physician and epidemiologist trained in public health and epidemiology at the CDC in Atlanta, formerly Chair of the Council on Scientific Affairs at the American Medical Association, and I am also the North American editor of the British Medical Journal.

DR. SOX: Thank you very much, Dr. Eddy, and Dr. Davis.

We are now going to hear from Harry Burke from New York Medical College. Welcome.

Harry Burke, M.D., Ph.D.

DR. BURKE: Thank you, Dr. Sox.

I am a consultant to HCFA, and I have no conflict of interest.

[Slide.]

I would like to begin by saying I am going to try and make two points in my presentation. I will make it brief because most of the panelists I think know pretty much what I am going to say.

But the first point is, is that much of what is going to come to HCFA has not been FDA approved, approved in the formal process, so the evaluation of safety and efficacy has not occurred prior to the request coming to HCFA. So, there is an adequacy of evidence required to establish at least that threshold because if the test, device or treatment is not effective, then, there is clearly no comparative

benefit that it can have.

So the adequacy of evidence must first be adduced to that if it has not received FDA formal approval, and then secondly, the adequacy of evidence must be adduced for what I call its comparative benefit.

So, with that said--

[Slide.]

So, I am going to talk about comparative clinical benefit levels of evidence and presentation of evidence.

[Slide.]

Comparative clinical benefit, also known as reasonable and necessary, can be defined as a test, treatment or device providing a measurable improvement over all the current relevant tests, treatments, or devices at a cost commensurate with the measured improvement.

So, I think what I would really like to do is frame this in a relativistic context, and that is, if you come to HCFA, you have to talk about comparative benefit, in other words, how does your test, device, or treatment do compared to what is out there now and where you have measured its comparative benefit rather than just assumed it.

[Slide.]

Now, clearly, FDA approval is prima facie evidence for safety and efficacy, but of course it is not evidence for comparative clinical benefit. The FDA makes no claims of comparative clinical benefit, and clearly, many tests, devices and some treatments are used without receiving FDA approval. Many of them are off-label uses, but those off-label uses may very well present themselves to the HCFA for payment.

[Slide.]

So, what would our comparative clinical benefit study look like? Well, generally, you would compare the test, treatment, or device to all the other relevant tests, treatments, or devices in terms of safety and efficacy if not FDA approved and in terms of clinical benefit.

So, the studies that are presented have to show safety, have to show efficacy, and have to be comparative in nature. Otherwise, how would you know?

[Slide.]

Now, an issue that always comes up I think are side effects, balancing the risks versus the benefits. Now, it seems to me there is two approaches to that. One is to look at the benefit of the intervention and weigh it to the risks associated with the intervention, but another approach I think which is out there as well is to compare the severity of the disease to the risks associated with the intervention, and I think these two weighting mechanisms are very different. I think they are almost different in kind and result in different empowerments in the process.

[Slide.]

So, who decides what the balance is between severity of illness and the risks of the intervention?

Well, I think the regulatory agencies may very well decide the magnitude of the risk if it is appropriate for the severity of the disease, but I think the patients should be empowered to decide if they are willing to accept the risk associated with the intervention.

In other words, individual patients should be allowed to decide if the clinical benefit of the intervention is commensurate with the risk given the severity of the disease which has already been taken into account in offering the test or treatment to the patient.

[Slide.]

Now, clearly, randomized prospective clinical trials that are large are optimal results, but as we know, you know, they are rare, the entry criteria limit the generalizability, there is some problems with reproducibility.

[Slide.]

So, I mean I think we all know the problems with RCTs - the cost, the length of time, how do you deal with relatively uncommon diseases, low event frequency, and ethical issues.

So, I would like to make the point that I am not sure that we can rely on large prospective RCTs for every decision that is made. We would like to. So, I would kind of like to rehabilitate retrospective evidence a little bit maybe.

[Slide.]

So, I would like to suggest that properly replicated studies by independent investigators may provide strong scientific evidence by confirming study results.

In other words, you know, if you go back to the scientific method, the scientific method relies on replication for adequacy of evidence, can the study be replicated by independent investigators, and more importantly, was the study properly done and then replicated by independent investigators.

I think the real problem with retrospective studies is that properly done, you know, dealing with the various biases that can creep into a retrospective study, but I think we are sophisticated enough today in our methodologies that I think that we can deal with many of the biases of retrospective studies.

Ten, 20 years ago, you know, when RCT--well, 30 years ago, when RCTs were coming to the fore, it was clear that our statistical and epidemiologic knowledge wasn't sufficient to deal with the retrospective evidence, but I think we have come a long way since then.

[Slide.]

So, I would like to propose three adequacy of evidence levels - strong, moderate, and weak. Now, clearly, a large properly designed, implemented and analyzed prospective randomized clinical trial is strong evidence for safety and/or efficacy and/or comparative clinical benefit.

[Slide.]

But I would like to suggest that failing that, if that is not always possible, that a large properly designed, implemented, and analyzed retrospective clinical study replicated by independent investigators also in a large properly designed and implemented, and analyzed would also be strong evidence.

[Slide.]

Of course, two, medium sized randomized prospective clinical trials where one replicates the second would, of course, be strong evidence.

[Slide.]

Now, moderate strength of evidence, a medium sized RCT I think gives us a moderate belief. We have all seen how medium sized clinical trials have not always been consistent when they have been reproduced, so we can't really say that that is terribly strong evidence, because it has been overturned relatively frequently, but still in a very small minority of cases.

[Slide.]

A large properly designed and implemented retrospective study that has not been replicated would only be moderate evidence in this setting.

[Slide.]

A medium sized RCT that is replicated I think would add strength to the findings, and would at least

give the appearance of a moderate strength.

[Slide.]

Weak evidence. I think small properly designed, implemented, and analyzed RCT, I think they are now recognized as relatively weak evidence. One of the reasons for meta-analyses is simply because small RCTs just don't do the job today that we would like them to do.

[Slide.]

Any retrospective study that is not large and hasn't been replicated would, I think, be weak evidence.

[Slide.]

Insufficient evidence. Small systematic studies, I call them exploratory rather than evidence. Case series are clearly anecdotal. Any study, no matter how big or what manner in which it is done, if it's not properly designed or implemented or analyzed, it cannot be used as good evidence.

[Slide.]

Well, "large," I define as 500 subjects, medium is 250 to 500, small is less than 250.

[Slide.]

I think that in this domain of HCFA, I think that many times medical supplies and devices, they are not tests or medications, they are relatively simple to assess, for example, a wheelchair, and I think they only need to demonstrate functional equivalence and equivalence in price in order to meet some evidentiary standard.

So, I think there are two things going on. They are the tests and medications which clearly require a higher standard than simple devices like a wheelchair.

[Slide.]

There is a real problem with presentation of evidence. One of the things that I have seen here at HCFA is when people come to HCFA and present evidence for a particular position, they don't present it many times scientifically. They present an ad hoc juxtaposition of many different types of studies, all the way from raw data to abstract to various types of publications, and I think that there really has to be systematicity in the actual presentation of the evidence to HCFA, because it shouldn't be HCFA's job to try and make sense out of a hodgepodge of stuff. It should be the person who is making the proposals job to create a cogent argument.

Any questions? Yes.

DR. FRANCIS: On the Drugs, Biologics, and Therapeutics Panel, when we reviewed the myeloma studies, we were specifically told that we were not to look at cost. So, one element of the comparative clinical benefit analysis that you just put up there dropped out. I wonder if you have any comments on that.

DR. BURKE: No, I did not consider cost either in my presentation, that's correct, so that would have been beyond the scope of the science involved in my presentation and move more into the politics of the process.

DR. FRANCIS: I thought your definition of comparative clinical benefit was measurable improvement at commensurate cost.

DR. BURKE: Yes, but I am not defining the cost aspect of it at this time. I am leaving that to HCFA, the cost comparison.

DR. SOX: I would like to ask Dr. Hill to comment on the issue of cost.

DR. HILL: I can confirm what Dr. Francis is saying, that we do not consider costs as part of this equation as we are currently working the decisionmaking process.

DR. BURKE: Measurable benefit, if you can measure the improvement in something and then later on just deal with the cost.

DR. SOX: Dr. Eddy.

DR. EDDY: Thank you, Dr. Burke.

I want to make sure I understand your definition of clinical benefit. Did you say that it requires measurable improvement over the current relevant tests, and a later slide talked about all relevant alternatives?

Does that mean that if something is effective, but not quite as effective as another treatment that is already out there, then, it does not have clinical benefit by your definition?

DR. BURKE: That would be correct.

DR. EDDY: So, if TPA had come out first, then, streptokinase would not have clinical benefit?

DR. BURKE: Well, again, you are addressing the cost?

DR. EDDY: No. Let's just assume that TPA is a little bit better than streptokinase.

DR. BURKE: That is correct. Duplicating what is already out there with a less effective agent would not be a measurable benefit, that's correct.

DR. EDDY: So, the benefit is always defined in terms of a comparison with an existing technology, not in terms, by your definition, not in terms of a comparison with the natural history or the untreated condition or a placebo.

DR. BURKE: That's correct.

DR. GARBER: This is really by way of clarification. Your highlighting suggested that in the study designs that were "less than clinical trial," like the retrospective studies, the key issue is replicability, but your language earlier in the sentence says that involved replicability, said properly designed, and I am hoping that you will clarify for the committee what you meant.

I think a prime example of the problem here is the studies of hormone replacement therapy for postmenopausal women where there are a number of fairly well designed observational studies that were quite consistent and remarkable consistency among a large number of studies showing that it prevented heart disease and lowered all-cause mortality, and the first randomized clinical trial contradicted all of those.

So, perhaps you could clarify your ranking of the design issue versus replicability.

DR. BURKE: Right. I mean if, in fact, everything can be assessed by an RCT, then, I think that is clearly the way to go. Okay. But the issue I am addressing is what if it can't, what are you going to do then. Okay.

So, I am not saying that they are comparable theoretically, clearly, they are not, but in the practical world in which we deal with, it is not always possible to have a large RCT, and if it is not possible, then, what do you do, what is your adequacy of evidence at that point, and that is the issue I was stressing.

DR. FERGUSON: If I understand correctly, a well conducted randomized clinical trial with 249 people in it would be weak evidence.

DR. BURKE: I am not determining how many hairs makes a bald man. I mean the 250 is a relatively arbitrary number. What I am trying to do is make a distinction between large, medium, and small, and whatever the committee thinks those numbers should be is fine.

I was just trying to put something down, so we had some frame of reference.

DR. SOX: Dr. Eddy.

DR. EDDY: I would like to ask you a few more questions about the role of retrospective studies. As I listened to you, I didn't hear you say anything about controls in the retrospective studies, so you are including retrospective studies that have no controls, like a review of records, the clinical series.

DR. BURKE: I am suggesting it has to be properly designed, and I am not specifying the proper design. I am just suggesting that if it can't be properly designed, it shouldn't be done, and/or if it is done, it shouldn't be good evidence.

DR. EDDY: So, the issues about what the proper design of a retrospective are still open.

DR. BURKE: Exactly, and I think that is something that the committee probably has very strong thoughts about.

DR. EDDY: One more question, if I may.

Let's imagine that a randomized controlled trial could be done, but hasn't been done. It could be done, it is feasible, say, it takes two or three years or something like that, you can get the appropriate sample size, but let's say it has not been done, but let's imagine that there had been some retrospective studies of proper design, however we define that, but they are not randomized, so there are always remaining questions about random biases.

Let's imagine they had been replicated. Would you consider that to be strong evidence?

DR. BURKE: Yes, I would. In other words, if there are large, properly designed, dealt with all the potential retrospective biases that could occur in a study, was replicated by independent investigators in a separate population, okay, also properly designed and large, yes, I probably would.

DR. EDDY: I guess the question is whether you would know whether all the biases could be--

DR. BURKE: Right, and that's a judgment call, and I mean that is something that people have to actually look at the study design specifically on a study by study basis.

DR. SOX: Ms. Richner.

MS. RICHNER: The replication issue is important, too, in terms of who would ask or pay for replication of studies for evidence, for instance, for this coverage committee, et cetera, that is a question of mine, and then also the types of evidence that are going to be required, Dr. Eddy just addressed my concern, whether or not retrospective data would be--

DR. BURKE: I think that it is up to the person, as Ron pointed out, it is up to the person, the group proposing that something be paid for, that they provide adequate evidence. So, the standards for adequacy have to be out there, and they have to decide whether they believe that they meet those standards.

MS. RICHNER: And this would forego FDA requirements or be beyond what the FDA would require.

DR. BURKE: They would have to meet efficacy standards. If they have not been met, they must meet them, and this is a really critical issue because at our last meeting, we spent all our time on efficacy, and nothing on comparative benefit, okay, because it had not been established, efficacy had not been established, so that is a really, really important issue if it hasn't been established already.

DR. SOX: Dr. Holohan.

DR. HOLOHAN: Let me get back to point that Dr. Eddy had raised that I would like a little more detail on.

You had made the statement we have techniques today to deal with biases. Virtually all case series or retrospective studies have biases, unintentional or otherwise, and we have kind of glossed over how we deal with those biases.

Let me give one example. Large retrospective studies replicated, that are in fact in a different patient population, for example, evidence submitted to Medicare based on retrospective studies where the oldest patient was 55, and we know that there aren't very many Medicare beneficiaries who are that age group.

How can we extrapolate that intrinsic bias of the study and come to any conclusion as to whether, in fact, it applies to the population we are concerned with?

DR. BURKE: I don't believe that retrospective studies are the best standard of evidence, let's be clear about that, but I think that in the real world, they are going to wind up being a standard of evidence whether we like it or not, and the issue is I think 20, 30 years ago, we didn't know most of the biases that could creep into retrospective studies.

Today, we know, I think, most of the biases that can creep in, and I think we can evaluate the studies and see if they were able to deal with those biases, and if we believe that they were not successfully able to do so, then, it is not a properly designed study.

DR. SOX: I am going to ask for one more question, then, we will move on, and we will get a chance to get you up here again and ask you questions during the open session.

Daisy, why don't you go ahead.

DR. ALFORD-SMITH: I just wanted really for you to repeat what you had talked about in reference to medical supplies.

DR. SOX: Could you repeat the question?

DR. BURKE: The question is, is medical supplies and devices, and my point was, was that cotton swabs, for example, or wheelchairs, if they are functionally equivalent, I don't think that we should apply a high level of evidence requirement in order to pay for a different swab or a different wheelchair assuming that there is functional equivalency demonstrated.

DR. SOX: Dr. Garber, a brief clarification?

DR. GARBER: I will skip my real question, but just to the point of clarification. When you say "retrospective," I believe you mean any kind of observational study, not solely retrospective, including prospective registry, et cetera.

DR. BURKE: Right.

DR. GARBER: Thank you.

DR. SOX: Thank you very much.

One of our members has arrived a bit late. Would you introduce yourself, say where you are from, what you do, and whether you are a voting member or a consumer rep or manufacturer's rep.

DR. PAPATHEOFANIS: I am Frank Papatheofanis. I am a faculty member at the University of California, San Diego, in the Department of Radiology. I am the vice chair of the Diagnostic Imaging Panel, and I am a voting member.

DR. SOX: Thank you very much.

Before we move on to the open public comment section, I would like to suggest where we ought to be going. One of our jobs is to provide guidance to the panels and to coordinate the panels, and in respect to the issue of standards of evidence, I think this could mean probably two things and will.

One is some form of written expectations or principles of the type of evidence that is required in order to make a recommendation for coverage, and the second is what might be called case law. That is, it is our comments on the proposals for coverage that come to us, and I suspect that over time the combination of some sort of upfront written expectations about the standards of evidence and the so-called body of case law that we develop as a result of our comments as we will undoubtedly do this afternoon, will make up the form of guidance to the panels that will enable them to function effectively.

So, I think in general that is where we are going. Early in the afternoon, I am hoping that somebody on the panel is going to give us a written proposal that we can discuss and vote on, so that we can begin the process of helping our panels to function in a roughly similar way across all panels.

So, with those brief comments, let's move on now to an open session, and we are going to have two speakers. Each are going to speak for 10 minutes, and we will have time for questions after each speaker.

I would like to remind each speaker that they should state if they have any financial obligations with the manufacturers of any products being discussed or with their competitors.

We will start with Dr. Greg Raab from the Health Industry Manufacturers Association.

Open Public Session

Greg Raab, Ph.D.

DR. RAAB: I would like to be accompanied by our counsel, Brad Thompson, from Baker & Daniels.

Thank you. My name is Greg Raab. I represent the Health Industry Manufacturers Association. It is a pleasure to speak to you this morning at the first meeting of the Executive Committee.

I am particularly pleased to be here because the Payment Committee of HIMA's Board of Directors has been discussing this week the very issue that you are considering this morning.

Before I share with you HIMA's views on Medicare coverage criteria, I want to applaud the considerable progress that HCFA has made over the past year in establishing a more transparent and predictable national coverage process.

The chartering and the establishment of the MCAC, and the publication in the Federal Register of a coverage process notice, help give the public an understanding of at least the basic rules of the road of Medicare coverage.

In addition, I want to thank MCAC for fostering an open coverage review process by providing ample time at panel meetings for beneficiaries and outside experts to speak. This assures that beneficiaries have a voice in these decisions, and HIMA encourages MCAC to continue this pattern of openness in upcoming panel meetings.

Given the credentials of this panel and the pivotal role MCAC plays in the coverage decision making process, I am most certain that you already appreciate the fundamental importance of coverage criteria.

These criteria will directly influence the capacity of many medical device companies to undertake and

develop new products because HCFA's data demands will directly affect the cost, length, and likely success of the innovation process.

As you know, Medicare's coverage criteria have not been spelled out for the public, and HIMA believes that they need to be made explicit. HCFA announced in its April 27 coverage process notice that it will undertake formal rulemaking to establish coverage criteria.

Originally, we expected that a proposed regulation would be published before the first MCAC panels began meeting. This obviously did not happen, and while HIMA appreciates how acutely the MCAC panels must feel the lack of coverage criteria as they hold their first meetings, we nevertheless must stress the importance of following formal rulemaking in crafting these standards.

I want to emphasize to you that the proper forum for developing these coverage criteria for the Medicare program is the federal rulemaking process, not the deliberations of this advisory committee.

The rulemaking will allow for broader public exchange of ideas to shape an appropriate set of substantive criteria, well beyond what can occur in this room. This is particular important given the sharply divergent views that, in all likelihood, exist on this subject.

It would seem incongruous for HCFA to issue any directives at an MCAC meeting regarding the agency's views of the "proper" substantive criteria to be used without first allowing for public input pursuant to the rulemaking requirements. HCFA must be diligent to avoid tainting the public process or using the podium to announce what are, in effect, substantive rules.

In addition to the risk that HCFA might prematurely announce new rules that should first undergo rulemaking, we are concerned that HCFA is not properly using the MCAC Executive Committee.

The MCAC charter and the HCFA policy statements make clear that MCAC is set up to offer advice to HCFA on technical matters - it has not been established to recommend policy for the agency. This body should not develop, nor rule upon, the criteria that the various MCAC panels are supposed to apply.

We applaud HCFA for undertaking rulemaking to develop national Medicare coverage criteria, and we hope that the agency will allow the rulemaking's public process to go forward as intended, without extra-procedural influences that may indicate agency prejudgment.

I would like to at this point pause in my statement before I get into a few specific guidelines as Medicare coverage, what we think Medicare coverage criteria ought to be, and ask our counsel to comment on the proceedings. Brad.

MR. THOMPSON: I apologize. I am from Indiana, so I speak very bluntly, and I will speak bluntly to you now.

I think this panel is in a bit of a predicament, and that may be an understatement actually. There are a number of federal requirements that apply to how these policy issues get resolved.

Greg just explained to you that there is an ongoing rulemaking, and the rulemaking is a very public process that goes well beyond this room. That rulemaking is the place to ventilate these issues. Doing this kind of discussion before that rulemaking is completed in effect short-circuits the rulemaking, and that just isn't allowed.

To be very specific and very practical about this, the presentation that you just heard from Dr. Burke--and I am not picking on Dr. Burke here--but I assume that he is speaking on behalf of the agency, I see him listed as the HCFA presentation, and he described himself as a consultant, so I assume he has the mantle of the agency, and his remarks were in some fashion pre-cleared by the agency.

Those remarks are very problematic for two reasons, not the least of which is the Administrative Procedures Act, but more fundamentally, the fact that a lot of what he and the agency are advising you on in that presentation is legally incorrect.

His description of the federal Food, Drug, and Cosmetic Act is simply legally incorrect. His description of the impact or the proper criteria for reasonable and necessary, the requirement, for example, that new technologies be better than existing technologies is legally incorrect.

Now, if this were rulemaking, we would file elaborate written comments and cite all the law and provide you with our analysis. You take it back, you would read it, and you would study the act yourself, and you would reach a conclusion. You can't do that here. That is why the rulemaking is more suitable for resolving issues like what the criteria and the evidence ought to be.

I also heard price discussed in the context of it, and Dr. Burke clarified that he wasn't offering an opinion on cost effectiveness. It was in the remarks, it was in it a couple different places, and I would urge you to disregard cost at this juncture because that is very problematic and most likely illegal.

So, the predicament that you are in is everybody is assembled here, I know you want to get some business done, there are valuable things that you can do, but outlining--and Chairman Sox, I am referring specifically now to your objective of the day of coming up with a written concept of what the evidence ought to be--that objective is very problematic.

You can certainly share thoughts about what the different panels are doing, the issues that they are facing, trying to figure out ways to harmonize the decisions that you are making right now, but coming up with proscriptive requirements for future decisionmaking short-circuits the public process.

That's all.

MS. LAPPALAINEN: I would like to remind the speakers please state your name.

MR. THOMPSON: I apologize. Greg introduced me. I am Brad Thompson with Baker & Daniels, and I do have a financial interest because I am engaged by HIMA.

MS. LAPPALAINEN: Thank you. And if you could also please state the mission of the Health Industry Manufacturers Association?

DR. RAAB: The Health Industry Manufacturers Association is a trade association representing more than 800 manufacturers of medical devices. It is based in Washington, D.C.

MS. LAPPALAINEN: Thank you.

DR. SOX: I just want to remind you that his time counts against your time. You have got about seven more minutes.

DR. RAAB: About seven more minutes? What I would really like to do at this point is highlight a few of the key principles that HIMA believes should be included in the Medicare coverage criteria regulation. We hope that these principles will guide HCFA as it develops a proposed rule, and we think that, taken together, these principles might serve as a useful yardstick against which the proposal can be assessed.

First, HIMA believes that coverage criteria should put the patient first. This means a product's clinical effectiveness should be the determining factor for HCFA in judging whether a product is "reasonable and necessary," and covered by Medicare. We believe this because this judgment, whether or not to provide beneficiaries access to a product or service, is fundamentally a patient care decision.

Economic factors should play no rule in this decision. Coverage decisions should not be used as a way to limit overall Medicare expenditures, this budgetary role is reserved to the Congress. It is the Congress that allocates the funds for Medicare's payment systems.

Let me be emphatic on this point. We see nothing in the Medicare law giving HCFA authority to make coverage decisions based on economic information. As you go about your work advising HCFA on coverage decisions, you should be guided by the clinical effectiveness of a product or service, not its cost or its cost effectiveness. Economic factors are more appropriately considered in the context of payment.

Let me stress also that the coverage determinations you help HCFA make can be undercut if HCFA's coding and payment systems do not result in timely decisions and fair reimbursement for the technology or service in question.

We at HIMA are concerned that beneficiary access to covered services is sometimes placed in jeopardy because these technologies are not properly integrated into the Medicare program.

Second, HIMA believes that clinical evidence used in making coverage decisions should be reasonable, clinically relevant, and collaboratively developed.

HIMA believes that the evidence gathered as part of the FDA review process to demonstrate a new product's safety and effectiveness should in many cases be sufficient for Medicare coverage. This has been the case in the past, and we expect the new HCFA rule to recognize the importance of this information.

Further, we believe that Medicare should not duplicate FDA's review. HCFA should not reconsider, or otherwise challenge, an FDA determination that a product is safe and effective.

With respect to other data that may be required for coverage decisions, HIMA believes that these requests should be grounded in common sense. HIMA believes that HCFA should certainly ask for the data it needs to determine that a product or service is reasonable and necessary for patient care, but it should avoid demanding excessive or unrealistic amounts of data.

If HCFA demands more than is truly necessary, the data themselves, in a sense, become a hurdle to innovation. For this reason, HIMA recommends that specific evidentiary requirements be developed with the involvement of clinicians and product innovators. Further, these requirements should be tailored to the medical treatment, technology, or procedure under review.

Evidentiary requirements should also take into account the practical impediments, that is, the time involved, the cost, and the patient impact, to the development of this information.

With respect to hierarchy of evidence, which was discussed earlier, HIMA believes that the clinical evidence used in making coverage decisions should be marked by the same innovation and flexibility that mark the technology development process itself.

This means that technology assessments, based on peer reviewed randomized clinical trials, may not be the best way to assess the clinical merit of a new technology, and that ways must be found to solicit the input and experience of practicing physicians, the insights of medical specialty societies, and the experiences and observations of the inventors themselves.

Agency for Health Care Policy and Research Director John Eisenberg summed up this point nicely in a recent article in the Journal of the American Medical Association. I would like to quote from that article.

"Those who conduct technology assessments should be as innovative in their evaluations as the technologies themselves. There is little argument that the randomized clinical trial is an accepted high standard for testing effectiveness under ideal circumstances, but it may not be the best way to evaluate all the interventions and technologies that decision makers are considering."

Eisenberg concludes by saying that "the randomized trial is unlikely to be replaced, but it should be

complemented by other designs that address questions about technology from different perspectives. Researchers need to develop and test new ways of evaluating technologies that can be accomplished quickly and can take advantage of emerging databases and information needs."

Third, HIMA believes that Medicare should amend its current policy on investigational devices subject to investigational device exemptions at the FDA by making payment for all Category B non-experimental or investigational technologies.

This would eliminate the current uncertainty that exists regarding whether or not these products--which represent incremental as opposed to breakthrough improvements--are made available to Medicare's beneficiaries.

Fourth, HIMA believes that HCFA should not make national non-coverage decisions until it has definitive information that the product or service is not effective or that it causes patient harm.

National non-coverage decisions can cut short the development of valuable clinical information.

Finally, HIMA believes that coverage restrictions, through appropriateness reviews, when necessary, should be well grounded in clinical evidence and frequently updated.

HIMA recognizes that HCFA will occasionally decide to set limits on the availability of a covered technology or procedure to ensure what the agency believes is appropriate use.

HIMA believes that HCFA should establish such limitations only if they are supported by medical evidence, and only if the restrictions are consistent with the advice of medical specialty societies. Further, HIMA believes that HCFA should make available to the public the rationale and justification for any restrictions it imposes.

Given the rapid pace of change in the technology industry and the way care is delivered, coverage restrictions must be updated frequently if they are to remain clinically relevant. Coverage limitations should be updated or revisited annually at least if they are to be kept in effect.

This concludes my presentation. Thank you for permitting me to share with you HIMA's views.

DR. SOX: We have got about a half-hour to complete the open public session. I think I will entertain about 10 minutes for questions or comments on Dr. Raab's presentation.

Dr. Hill.

DR. HILL: Thank you. I hope it is understood that our choice not to engage in debate with counsel does not imply our agreement with his assertions necessarily or our disagreement.

While I don't want to engage in that kind of interplay because it involves him personally, I would ask the Chairman's indulgence if Dr. Burke could clarify his situation and whether or not his remarks were pre-cleared and if you would go to the microphone and state whether or not this was an independent suggestion you made.

DR. BURKE: This is an independent assessment of adequacy of evidence for HCFA. I was not speaking--thank you for giving me the opportunity to clarify that--I was not speaking for HCFA when I made my remarks.

DR. HILL: Thank you. Last, if I may, would you care to offer, Dr. Raab, a suggestion as to where in the hierarchy of evidence you think these more creative or these more novel forms of evidence should lie?

DR. RAAB: Hierarchy is a difficult term. I think there is a range of evidence heights that fit and should be used. The word "hierarchy" implies that one is better than another. What might be best for a particular technology, in a particular circumstance, might not fall at one end of the scale. Items should be considered appropriate for the technology.

DR. SOX: Dr. Eddy.

DR. EDDY: I am going to ask two questions which I hope can be answered very briefly, because I want to make--I am going to start with this one.

I am looking at your fourth recommendation, which if I read it correctly, has huge implications. Basically, it flips what is the common burden of proof.

Do I hear you or do I read this correctly that something should be covered unless there is good evidence that it is ineffective or causes harm?

DR. RAAB: I don't understand your point.

DR. EDDY: Would you repeat the fourth principle for us?

DR. RAAB: HIMA believes that coverage restrictions, when necessary, should be well grounded in clinical evidence and frequently updated.

DR. EDDY: No, I am sorry. HCFA should not make a national non-coverage decision--

DR. RAAB: --should not make national non-coverage decisions unless it has definitive clinical information that the product or service is not effective or that it causes harm.

DR. EDDY: So, is that a recommendation that something would be covered unless there was evidence

that it was not effective or caused harm?

DR. RAAB: It is a recommendation that HCFA view the importance of a national non-coverage decision, that there is a sense in industry that in the past, HCFA has made national non-coverage decisions which have headed off, stopped and halted the development of information, that there was no information saying that there was any harm or problem.

For instance, products may be reviewed locally. Medicare contractors could be covering costs. HCFA might understand that that is happening and issue a national non-coverage decision which would halt this coverage.

DR. EDDY: Let me rephrase it. Let's imagine that there is an intervention, and there is no evidence yet of safety or effectiveness. Are you recommending that HCFA should cover that or not cover it?

DR. RAAB: There is no information on safety and effectiveness?

DR. EDDY: There is no information on safety or effectiveness.

DR. RAAB: I think a better situation would be an FDA-cleared product that is considered locally by a Medicare contractor. It is covered there, but in absence of a national Medicare decision.

DR. EDDY: I will try once again. Let's say it is not in the jurisdiction of the FDA, so it's a device. There is no evidence of safety or effectiveness. Do you think it should be covered? I am just trying to understand the principle that you are recommending to us.

DR. RAAB: I guess I am not tracking with your question. Brad, do you understand this?

MR. THOMPSON: I think so.

MS. LAPPALAINEN: For example, what if we have an exempt device in front of us for a coverage decision. This is a device that is, by law, exempt from the FD&C Act.

DR. RAAB: There is two elements to this. One is there are exemptions to the federal Food, Drug and Cosmetic Act for products which, in the view of Congress, don't require safety and effectiveness data to be lawfully marketed, because they don't pose a risk. In that case, I would say that there is some evidence there is at least a congressional determination that this product falls into that category.

But the second and more important element to your question is remember there is three potential outcomes - there is national coverage, there is national non-coverage, and then there is hands off and allowing the local process to make the decisions.

The point of this bullet point is that if this committee doesn't have evidence which suggests that it is unsafe, it ought to allow the local process to continue to decide whether or not to cover it.

So, we are not saying it is automatically covered. We are saying this committee shouldn't elevate it to a national decision and make a national non-coverage decision. It should let it continue to percolate through the local system and let the local contractors decide whether or not to cover it.

DR. SOX: That is a pretty clear answer to your question.

DR. EDDY: I now understand the answer.

DR. SOX: Dr. Francis.

DR. FRANCIS: I want to press you on the distinction between a policy judgment, which you think requires notice and comment rulemaking, and a technical judgment. Maybe the way to do that would be to start just by asking you about some of the points in Dr. Burke's presentation.

Would, for example, the size of a randomized clinical trial, whether it's a small trial, if it's under 250, for example, be a technical or a policy question, and then maybe you could go on to the issue of some of the classifications as strong, weak, or moderate strength.

Again, are those the kinds of choices that you are advocating should be subject to notice and comment rulemaking or are they technical?

DR. SOX: I just want to remind you that you have got four minutes until the end of the discussion period.

DR. RAAB: I will be brief. In the law, the dichotomy between rulemaking and not rulemaking is not policy versus technical, so I am afraid I can't answer your question directly because that is not the legal framework.

The legal framework is whether it is a substantive rule or not. It becomes a substantive rule if it is prescriptive. So, if the agency said there must be 250 individuals in a trial, that is prescriptive, that is a rule, that requires rulemaking.

If a group of scientists are debating relative size and power of a study, and don't lay out prescriptive requirements, that is a technical discussion, and that doesn't require rulemaking. I hope that is responsive.

DR. EDDY: Can I try one more quickly?

DR. SOX: Please do.

DR. EDDY: This is a question to Mr. Thompson.

I think you said that it might be illegal for the panels to consider cost.

Did you mean that and, if so, what is the basis for that?

MR. THOMPSON: Part of the difficulty here is that this discussion is premature. My law firm is engaged right now in writing a legal brief on whether cost is a permissible item to consider under the reasonable and necessary standard.

Thus far, I can tell you, and there is thousands of pages of legislative history, thus far, I can tell you that it is our opinion that Congress did not intend cost effectiveness to be considered in the context of reasonable necessity.

I have not yet finished my legal analysis. By the time the rulemaking rolls around, I expect to have it done, but as of right now that would be my assessment, but it is a preliminary one.

DR. SOX: Briefly.

DR. EDDY: So, would this mean that--let's imagine that a technology did not meet Dr. Burke's definition of clinical benefit, that it was effective compared to no treatment at all, but wasn't quite as good as some other product that was out there, but it was much less expensive.

Would this say that we could not consider cost effectiveness?

MR. THOMPSON: Well, see, the other part of your scenario is that this comparability issue, that that is a basis for the decisionmaking, and I heard Dr. Burke say that new technologies needed to be superior to existing ones.

I would challenge that opinion, as well, on the basis of the law, that new technologies do not need to be superior, they can merely be comparable. Sometimes you can come up with a more or less equivalent mousetrap, and that equivalent mousetrap ought likewise to be covered.

So, there is a couple of different elements to your question, and I would say that if it's in the realm of clinical comparability, not superiority, it ought to be covered regardless of cost. The cost element comes in later in the equation, and the agency has a lot of tools in the payment arena to decide how much it will pay for a technology, but that is a conceptually separate issue.

I am not saying cost is irrelevant. I am just saying is occurs at a later point in the regulatory process.

DR. SOX: Thank you very much. I think we will close the discussion period from your presentation.

Linda?

DR. BERGTHOLD: I would like to get him to clarify this high level of evidence issue.

Are you saying that if there is a large randomized controlled trial, that there would be any situation under which that would not be the best level of evidence? You talk about creativity of evidence sources, but if you have a large RCT, is that not the best level?

DR. RAAB: An RCT, if it is available, should be used. The issue is in a coverage situation, to demand of a product sponsor upfront sorts of data, when other data may be available and just as good to make the decision.

DR. SOX: Thank you.

We will move on. Dr. Larry Weisenthal from the Weisenthal Cancer Group will be the next commentator. I would just remind you to disclose any financial involvement that you may have.

Larry M. Weisenthal, M.D., Ph.D.

DR. WEISENTHAL: My name is Larry Weisenthal. I am a medical oncologist in Huntington Beach, California. I am essentially in a laboratory-based private practice. I am entirely self-supported. I do have a conflict of interest in that I provide one of the services that has been under consideration by MCAC.

DR. SOX: Sir, do we understand that your remarks are going to be general now and then later--

DR. WEISENTHAL: I am going to address that in my introduction.

DR. SOX: You do have allotted time for discussion of the issue of tumor--

DR. WEISENTHAL: Yes, I discussed this with Sharon Lappalainen before making my talk, and I understand the purpose of the morning session, and I will try to stick with the spirit of that.

In his presentation, Ron Milhorn, one of his slides showed that not all types of medical evidence of medical effectiveness are appropriate for all services, and he kind of went by that quickly, but I think that is important.

The idea is that you can make these decisions very mathematical, as Dr. Burke is quite able to do, but everything needs to be considered in context. There is four specific issues that I want to cover in my remaining nine minutes.

One is the idea that you need to compare the levels of evidence relating to the new method as contrasted

with the levels of evidence which exist to support the old method. In other words, it is not fair only to consider what is the evidence that supports the new, but how does that compare with the evidence that supports the old.

Secondly, it is very important to define the relevant dataset of evidence to consider, and this particularly applies to a situation in which there exists not, let's say, just a few pieces of evidence, so you are going to consider everything, but rather you have a large array, let's say, 100 different very small studies.

So, the question is which of these data are relevant, which should be included and which should be excluded. I think in the MCAC meeting earlier, all of my complaints relating to that have to do with the fact that there was not an agreement on which was the relevant dataset.

Honest people can disagree over the interpretation of data and sometimes you just can't agree, but I think that in most cases, it is possible to agree in advance on what is the relevant dataset to consider.

I think that in the meeting that we just had, we could have, with just a little preliminary communication, both sides could have agreed that these are the relevant studies which should be included, these are the irrelevant studies which would should be excluded, and then the whole process would have been much more clear to the panel and I think more satisfactory to everybody.

So, I would urge that in the future, that in advance of the meeting, that there at least be an attempt to reach an agreement on what are the relevant datasets to consider.

Thirdly, it is very important to consider conflicts of interest in those presenting evidence, and there is a natural tendency to focus in on the conflicts of interest or proponents, such as me, who might have a commercial interest, but it is important to ask that question of everyone presenting evidence is there a conflict of interest.

Lastly, it is very important to consider the need for the service being proposed and therefore, to consider the risk in not providing an opportunity for the proposed service to compete with existing services.

Now, that is what I am going to cover. I will illustrate each of those points with an example from the service that I am here in the afternoon to represent, but the purpose in doing this is not to argue the issue, and I think you will agree that I am presenting a balanced presentation, but rather just to illustrate why each of these points is important.

Firstly, comparing levels of evidence relating to the new service compared to that supporting the old service. On Thanksgiving, I went down and had Thanksgiving dinner with my friend who is a gastroenterologist, and his wife was is a physician, too, and these are excellently trained physicians, Johns Hopkins, Case Western Reserve, Tufts, Boston University, well-trained physicians.

The husband, who is one of my best friends, I was the best man at his wedding, is a gastroenterologist,

and he performs a procedure called colonoscopy. Fifteen years ago, Medicare paid him $350 to perform a colonoscopy. Today, it is about $115, it has been cut down by two-thirds. $115 is about 15 percent more than a family practitioner gets to perform a flexible sigmoidoscopy. Flexible sigmoidoscopy is a very easy procedure, you only go in about 25 or 30 centimeters, whereas, a colonoscopy can be very challenging, you want to go in to 100 centimeters.

So, my friend told me something very interesting, and that is, that it used to be in the old days when they got paid $350, it was sort of a point of professional pride and responsibility that you tried to visualize the entire colon. This was very important, and if it took you 45 minutes or an hour, you did it.

Today, he tells me nobody does that. They figure they are getting 15 percent more than going in 30 centimeters, so their responsibility is to go in and do about 38 centimeters and if they encounter any problems and it takes them more than eight minutes, they just send the patient up to a barium enema.

What happens then? The patient has to undergo two bowel preps. Medicare ends up paying for two procedures, colonoscopy plus barium enema, and sometimes three procedures because the barium enema may then reveal a proximal lesion, and the endoscopist has got to go back in and rebiopsy that.

So, he was explaining this with a lot of bitterness, and he voted for Bill Clinton twice, he blames Bill Clinton somehow for this, so he says he is never going to vote for a Democrat again, but there is a lot of bitterness in his heart.

He tells me that he is in a multispecialty group and all the other specialists, the cardiologists, the infectious disease people, the endocrinologists, they are all having the same problem. They all hate medicine, they don't want their kids to go in it, and so forth.

Now, this is relevant to this consideration, because there is one exception. There is one group of specialists that he says are doing very well, and those are the oncologists. Why are they doing well?

Well, they are doing well for the following reason, that is that most chemotherapy in this country is given as an outpatient by oncologists in their office, and what happens is, is that they get reimbursed, not just for providing the service, but they get reimbursed for the drugs. The drugs are very, very expensive, and typically, with most insurance plans, they would get reimbursed by some formula relating to the average wholesale cost.

Now, those of you who know the oncology literature know that there is rarely a situation in which there is one form of therapy, and only one, which has proven effective, and particularly you get into second-line therapy, there is no situations where this is standard second-line therapy, and if you just look the PDQ, which the NCI publishes, which is supposed to be state-of-the-art treatment, you can find multiple different forms of therapy.

So, you could flip a coin and be equally well off or equally supported by the literature in choosing

therapy. How do they choose therapy? It is on the basis of the spread between the average wholesale cost and what they get reimbursed, so you have got a choice of drugs, and you are in an environment where doctors are getting killed or they are having trouble making their mortgage payments, much less saving up for retirement. And you don't think that that is going to enter into their decisionmaking? It does.

So, basically, the competing paradigm, the new thing that is being proposed, is you test the biology of the tumor, and you choose the treatment based on what is tailored to that individual biology.

The old paradigm is you either flip a coin or, more insidiously, you look at the spread between wholesale cost to reimbursement, and you choose it on that basis.

Now, what does it take to support Medicare reimbursement for a therapy? Typically, two papers published in the literature, these are not randomized papers, but let's say an oncologist wants to use gemcitabine in sarcomas. He just has to usually produce one or two papers showing that, yes, gemcitabine has been used in sarcomas.

This is the level of existing evidence, and I think that when you consider the new paradigm, you have to consider the levels of evidence relating to the new paradigm compared to the levels of evidence relating to the old paradigm.

Let's see, I have only got two minutes, so I really have got to hurry up.

Dataset is very important. I don't think I need to say anything more on that. It is just that it certainly is possible in advance to agree on a relevant dataset, and I will just leave it at that.

Conflicts of interest in those presenting evidence. There is the tendency to think that anybody that is providing a service wants to have it covered for his or her own selfish purposes. You want to have the service covered, so that you can get paid for it.

Certainly, that applies to things maybe like bone marrow transplantation, but it doesn't apply to everything. I daresay that you have very few ophthalmologists writing Medicare requesting coverage for refractive surgery for doing LASIK.

This is a procedure where you get paid $5,000 cash in advance, and these guys are getting rich off of it, and they don't want--you know, I doubt that there is any of those people that really want Medicare to cover it. I think in Europe, they pay $700 for the procedure, in the U.S., it is $5,000. Why should they want to have Medicare cover it?

Likewise, with respect to providers of the laboratory service. Some laboratories provide a relatively inexpensive service and coverage would definitely help them. Others provide a very expensive service, and because they have been in business, such as me, long enough, we have no trouble getting referrals,

and we just have the patients sign an advance beneficiary notice and we can then bill them whatever we want to bill them, and in the patients being in a desperate situation, will usually pay.

So, the thing to consider is, is that when you hear opinions from people that are providing the service, you know, it is not necessarily true that everybody that is providing the service wants to see it reimbursed, and there are individual reasons why someone might not want to have the service reimbursed, and you have got to look at that.

Now, when you look at people that aren't providing the service, such as, you know, that are giving testimony, such as the National Cancer Institute, universities and private practitioners, I was going to kind of take you through that and show you how the NCI had a conflict of interest in their testimony, how the universities have a conflict of interest in their testimony, and I already told you how the private practitioners certainly have a conflict of interest.

Why should they want to upset a system where they can choose the drug based on the spread, and thereby maximize their reimbursement? You know, why should they want to have a system in which, you know, they have to use a certain drug even if maybe they lose money on giving it, you know, if it appears to be best for the patient?

Then, the final thing that I want to say, and I can finish up really in 30 seconds here, and that is, the magnitude of risk in not providing an opportunity for the service to compete.

Dr. Bagley at the MCAC meeting made a statement with which I vehemently disagree, and Dr. Bagley stated that once Medicare makes a coverage decision to cover something, research stops, and there is a danger in covering it because then you just don't get any research done.

That may be true if you have something that is sort of universally accepted and everybody wants to provide. However, if you have got something that is controversial, so you have got competition of ideas and competition of technologies, the way to assure that the studies get done is actually to move the technology into prime time, so it is out there competing with existing technologies.

An example certainly would be the different ways of treating coronary artery disease, and you can do coronary artery bypass surgery, you can do percutaneous transluminal angioplasty, you can give statin drugs, you can now, I read, refer patients to certain clinics where they can be put on the Dean Ornish diet, 10 percent fat, and all of these are different ways of addressing the same problem, but there has been a lot of research done.

In other words, you know, by just approving coronary artery bypass surgery, that didn't make that the standard, I mean, so there really is a competition.

So, I think that in some situations, there is a huge need for a service, and if you don't provide coverage, you run the risk that it will never get the opportunity to compete.

The only thing specifically I will say about the service that I am a proponent of is to relate the following, and that is, that today, there is about 30 to 40 drugs available for treating cancer. Over the next 10 years, that number is going to explode.

There is fast-track FDA approval now, and what is going to be happening over the next 10 years is that you are going to have an ever-increasing supply of partially effective therapies. These therapies are very expensive, oftentimes very toxic. They are partially effective.

The budget crunch for Medicare is not in the year 2000, it is going to be in the year 2010 or 2015. There is going to be a crying need to be able to match the most appropriate therapy to the most appropriate patient, so that each patient gets the therapy that is individually the best for that patient.

These are orphan technologies, you know, they are not proprietary technologies, and I can go through all the reasons why you are just never going to have "industry" support for putting millions of dollars into the trials, however, if Medicare were to approve this, I guarantee you it would be the shot heard around the world, and it would stimulate the sort of definitive studies that everybody wants to see and for which there will be a crying need in just a few years.

Thank you very much.

DR. SOX: Thank you, Dr. Weisenthal. Sharon, do you want--

MS. LAPPALAINEN: Yes, I would like to make a point of clarification to the audience regarding the requirements for conflict of interest.

The conflict of interest statutes may be found under 18 U.S.C. and 5 U.S.C. The Federal Government and all Federal Government employees who are employed by the Federal Government must undergo conflict of interest.

This includes the special government employees who are here today on the panel. The Federal Government does not examine conflict of interest of sponsors or any non-federal employee.

Thank you.

DR. SOX: We have five minutes for discussion of Dr. Weisenthal's presentation.

Yes, Dr. Murray.

DR. MURRAY: Dr. Weisenthal, about 10 minutes ago we heard an exchange, the gist of which was that cost and expense are not to be considered in this decisionmaking. In 25 words or less, without going into detail, could you reconcile those comments with the basis of your argument, which seemed to rely

heavily on cost?

DR. WEISENTHAL: My argument relies heavily on humanitarianism, you know, seeing that a desperately ill cancer patient gets the best treatment for that patient.

My own personal opinion, what I heard was that a very sophisticated legal team was studying the legality of that. I don't know anything about the legality. My own personal common sense opinion is, of course, cost counts. I mean this is the year 1999 going into 2000, cost counts in everything.

DR. SOX: Other questions? I guess maybe I could ask one.

You said that, to some degree, our standards for making a coverage decision ought to be affected somewhat by the need for the service, and I guess my question is how do you know what the need is for the service unless you have good measures of the impact of the service on patient care outcomes?

DR. WEISENTHAL: Well, I think that this can be made very objective and mathematical, but it still requires some wisdom and common sense. The only way that I can answer that is just by giving an example relevant to the service that I am promoting, and the argument that I made was in this specific case, I don't know to generalize it, you have to consider each individual case, but I think that it is kind of like giving a student a grade. You give him an A, a B, a C, and a D, and how do you define what a B is and what a C is and what a--well, if you are a good professor, you know this is an A student, this is a B student. This is one of the situations you kind of know it when you see it.

I mean in this situation, even today we have, as I said, 30 to 40 different drugs which can be put together in hundreds of combinations. You can flip a coin and pick any one of them and find some support for it, and yet, 75 percent of all chemotherapy doesn't work, 75 percent of all chemotherapy that is administered doesn't benefit the patient at all.

In the second line situation, there are no studies at all to show population benefits any chemotherapy, yet, it is given all the time, and it is only going to get worse. As I said, the fast track approval, all the new biotechnology products, and so forth, mechanistic-based drug screens that are going to be bringing lots of things on the line, and these are expensive drugs, toxic drugs, and only partially effective, and there just has to be some rational way of matching treatment to patient, so I think the need is self-evident.

DR. SOX: Thank you. There are no more questions. Thank you very much. That will end the open public session.

At the suggestion of several of my colleagues, we are going to take a break now for 15 minutes. I would remind everybody that the cafeteria closes at 10:30, so those of you who need an extra shot of high octane coffee, this is your chance.

[Break.]

DR. SOX: I would like to go ahead and proceed. Actually, I would like to call on Dr. Hill to make a couple of clarifying remarks about the role of the Executive Committee in helping the panels to consider the evidence.

DR. HILL: Thank you, Dr. Sox.

I want to point out that there is a proscriptive element in what HCFA has to do. In our making of policy, we are guided by the--controlled by the statute, which says that no payment may be made for any expenses for services that are not reasonable and necessary for the diagnosis and treatment of illness or injury.

So, we do have to deal with threshold questions of what is enough evidence for something to be considered reasonable and necessary.

If the panel can tell us what it believes is an appropriate threshold for evidence that it would consider to be technically and medically efficacious, that would be valuable advice.

We are hoping that the committee will share with us, the individual members, as well as the thoughts of the committee as a whole, about what is an appropriate ordering of evidence.

All of the committee members look at scientific evidence and critically read articles in their own professional lives, as well as in their job here, and they all have ideas about what is a good study and what is not a good study, at a very minimum sharing that with us will be helpful.

Thank you very much.

DR. SOX: We will now proceed to a presentation by Alan Garber, a member of our Executive Committee.

Open Committee Deliberation - Levels of Evidence

Alan Garber, M.D., Ph.D.

DR. GARBER: If nobody objects, I will remain at my seat. I don't have slides to present, and I am hoping that we can use a good portion of my time for discussion.

A document has been distributed to the Executive Committee members. I am not sure if other people have received it. It is something I wrote called Standards of Clinical Evidence and their Application, and I realize now it is necessary for me to state that this document was not even requested by HCFA. This is something that I asked to have distributed.

I did inform HCFA that I was going to be producing this and this was motivated by the recognition that several of us have had that it is rather difficult to proceed as panels without having a set of criteria by which to judge evidence.

My document actually is not intended to be prescriptive, it is not that I don't have views about what we should do, but it is intended to describe what others have done, what some of the rationale is for developing standards of evidence, how that might work, and I do mention some options although I don't clearly state which ones I would favor, and it is intended to be that way because this is intended to structure discussion rather than to come to any specific conclusions. I hope that is an outcome of today's meeting.

Basically, I am not going to go through a summary of this document, but just to say that the reasons for having evidence standards as a key component of any process to either make coverage decisions, develop clinical guidelines, decide what is investigational and what isn't, they all have in common the idea that everyone benefits by having a fairly clear idea of what kinds of evidence are needed to draw conclusions.

Some of the reasons, of course, are transparency. The more specific and clear we are about what kinds of evidence we need to draw conclusions, the easier it is for everyone to understand the reasons for any decision.

It promotes consistency. If we say sometimes clinical trials, sometimes case controlled, sometimes this, sometimes that, there is no guarantee that a slightly different panel, composed of like people in the sense that they represent the same segments of society, will come to the same conclusion, so consistency is ordinarily considered a virtue, I think, for everyone concerned.

You can actually improve health care quality, adhering to high standards of evidence, of course, means that you are better able to avoid disseminating types of treatment, types of diagnostic procedures, and so on, that are ineffective and/or harmful.

I mention, not because it is necessarily relevant to our deliberations, but, in fact, using standards of evidence can be helpful in controlling health care costs in the narrow sense that by avoiding the dissemination of ineffective treatments, you have avoided expenditures on those treatments.

It promotes research. I am not sure I agreed with the quotation attributed to Grant Bagley that once a coverage decision is made, all research stops, but I certainly agree with the sentiment behind it. As anyone who has followed the saga of high dose chemotherapy for breast cancer can testify, it is extremely difficult to recruit patients for randomized controlled clinical trials once coverage has been made and once the belief is out there that a treatment is effective.

Of course, any decision we reach will be more credible and defensible if it is based on a fairly well defined set of standards for evaluating evidence. So, I hate to belabor these points, but I realize that not

everybody is in agreement necessarily that it is important to have standards.

Now, let me be clear, and I hope this comes through in the document, that believing in standards does not necessarily mean that you believe in rigidity, and, in fact, part of the art of this process is deciding when evidence is good enough and when it isn't, and, in fact, all of the speakers this morning I think alluded to the fact that sometimes something less than the so-called gold standard, the randomized controlled clinical trial, is going to be adequate and sometimes it isn't, and that's where the debate often comes.

Innovation was a word that was used in ways to analyze data, and in someone who has made a big bit of his career training people to innovate in methodologies for analyzing observational data, I believe in that very strongly, but a belief in flexibility and a belief in innovation is not the same as saying that there are no standards, and that is where the real issues become--and I don't think this is a policy issue, it is indeed a technical issue, it's a highly technical issue very often. It comes down to can you make a credible case that the biases in something that is not a randomized clinical trial are negligible.

Now, unfortunately, the ultimate answer to that are the biases significant enough to account for the result, say, a positive treatment effect, can't be known with certainty until after the fact, that is, a randomized controlled trial has been performed, and that is one of the reasons why we have so much difficulty because until we have had the randomized trial, we are going to some extent upon belief, and maybe our subjective estimates of how large biases are, but we are in a very difficult situation when we don't have a randomized trial, and I think that is what has been illustrated time and time again.

So, although we speak of a hierarchy of evidence, that may be an unfortunate use of the term because it does imply that there is one type of evidence that is always best, and although I think all of us agree that when you have a randomized controlled clinical trial that is directly involving the treatment of interest in the population of interest that is best, we rarely have that even when we have lots of randomized controlled clinical trials.

Then, we have to draw inferences from the population studied in the randomized trials to the population that will receive the treatment, and they can be very different, leaving us with some difficult decisions, and I think that we will be dealing with this very issue this afternoon.

So, a randomized trial in a narrow sense is indeed the gold standard, but rarely do we have the exact right randomized trial, so we are always dealing with evidence that falls somewhat short of perfection, and then, we, as an executive committee, and each of the panels has to deal with, well, what conclusions can we draw, when do we have adequate evidence.

The document that I have put together does not say under every circumstance what is adequate evidence, and I think we have to recognize as anybody who has participated in processes like this before, acknowledge that you really have to have some flexibility around some standards.

I had a very brief summary of types of evidence, but the types of evidence were well handled this morning, and I have asked to be distributed about a 100-page chapter from an Institute of Medicine publication about types of studies for evaluating technologies.

I would apologize for the length except that this does deal with the types of analyses and types of data that we will be confronting as panelists, and anything more comprehensive would be technical points at a minimum, so I thought this was the shortest document that would do, but I would refer that to everyone, and I hope it will be made available to the people who aren't on the panel who would like to see what has been distributed to the Executive Committee.

Now, as I said, I refrained from making any recommendations in this document that really describes what other--a big part of it is describing what other groups have done, but let me point out some areas of commonality, and for those of you who don't have copies of the document, among the groups whose approaches I tried to summarize, actually quoted directly from the documents were the Agency for Health Care Policy and Research, the U.S. Preventive Services Task Force, the Canadian Task Force on the Periodic Health Examination, American College of Cardiology, American Urological Association, the Blue Cross/Blue Shield Association, and there are many others. That is not meant to be a comprehensive list, but it is meant to be a sampling of what is out there.

One of the areas of commonality is they all have as part of their processes, some rating of the adequacy of evidence, and invariably, it is a two-step process.

One is you say is there enough evidence to draw conclusions, and the second step is what conclusions can you draw from the evidence once you have decided that the evidence is adequate to draw conclusions.

So, the first step is the rating of quality of evidence, and the second one is what are the results of your analysis of the evidence. I think it won't arouse too much controversy to say that if we are going to at least meet the standards of what everybody else is doing who has any credibility in this area, we have to at least adhere to those two steps - rating adequacy of evidence and then deciding what the evidence shows.

Let me propose in crude terms, then, and here I depart from the written document, a two-step procedure for us to follow. One is each panel should make a decision about whether the evidence is adequate to draw conclusions.

Now, I don't think that the Executive Committee should spell out in excessive detail what those standards should be. For example, we heard this morning from Harry Burke about small versus large randomized trials.

Well, as everyone knows, what is in a large enough clinical trial depends on a lot of things. It is not a specific number. Many of us think in terms of statistical power. We think about the consequences of

being wrong, what's at stake, and so on. So, we can't say as a rule, trials of 500 or more, or something like that, would be adequate.

We have to recognize that rarely is the evidence perfect, and in each case, we are going to have to have a discussion given the imperfections in the data about whether the imperfections are so severe that we can't really draw conclusions, do they call the major conclusions into question.

When we have a randomized trial, is it in the wrong population? Think about the economics of randomized trials. If you want to have a small sample size, which means a less expensive trial, you are going to pick the population with the greatest propensity to benefit.

So, the question becomes--and usually that is going to be a small fraction of the clinically relevant population, so let's say that you have established efficacy, and I underlined the word "efficacy" there because that is what most trials are about, they are not about effectiveness, that is how it works in the real world, you have established efficacy in that population.

Can we conclude that that means that this treatment will be effective in the population of Medicare beneficiaries? That is a question we will be dealing with over and over again.

Sometimes an observational study will be sufficient. For example, consider a condition that is known to be fatal within three or four months from the time of diagnosis 100 percent of the time.

We are not going to propose a randomized trial for a treatment that appears to work in that situation, but there is a trap here, and the trap is that very seldom do you have that situation, and in reality, most diseases are heterogeneous and you can't always be sure from observational data that everyone was going to die who didn't receive this treatment.

So, we have to be cautious, but yet open to the possibility that sometimes observational data can be compelling.

The second step I would propose is that we ask whether the treatment improves health outcomes. Now, there is the question of what is the benchmark against which we should measure health outcomes, and we have heard two views today. One is that it might have to be compared to no treatment at all, and the other is that it might have to be better compared to standard treatment.

I can tell you that in the world of clinical practice, as I am sure the other people from that world will agree, we look at something that is usually a broader definition of benefit, which is more or less I think what Harry Burke was saying, that the treatment offers some advantage, either it is less expensive or it is more effective, but it has to offer some kind of advantage, and to say that something is better than placebo, when other highly effective treatments are already available, it is just not sufficient to make me, as a physician, want to use some new kind of treatment.

So, we might want to consider something like an expanded definition of benefit, and I will leave it to the HCFA legal counsel about what we can do and stay within the regulations, but I think that in the world of medicine, what is relevant to us is does this treatment provide some advantage, and let me add, by the way, that when I say "treatment," I don't really mean treatment, I mean everything we will be considering - lab tests, screening tests, diagnostic procedure, and so on, and so forth.

So, that is really what I wanted to say, and I hope that we can have a discussion about how we might operationalize some ideas about evaluating the quality of the evidence, as well as how we would set criteria for what it is that makes something reasonable and necessary in operational terms.

DR. SOX: We have about 20 minutes for discussion. I guess the issue is, first of all, are these the right principles from which to proceed, and the second is how do we go about making these principles really useful guidance for our panels, so that we are all kind of singing off the same sheet of music.

Dr. Francis.

DR. FRANCIS: This may be even too early, but I would like to even backtrack you from what you just said to what panels got. I am not a physician although I can certainly--I have a scientific background to be able to read these kinds of things, but what we got was just an undifferentiated set of papers.

We did at one point get some effort to classify, but it came very late, and it seems to me one of the things, whatever else we do, one of the things that we should do is recommend a structure within which evidence goes out to panel members, because panel members had to cut through to even figure out which of the studies were randomized clinical trials, which ones were retrospective, which ones were--you know, nothing was in any way structured.

So, I would add as a recommendation that even if we don't get to the point of saying this is the best quality, this is the next best quality, that we at least say to the panel that when stuff goes out to panel folks, it has got to be tight.

DR. SOX: Perhaps I could comment. Based on the experience I have had running the ACP-ASIM process and the U.S. Task Force, in both of those deliberations, we had a structured background paper which, for the current U.S. Task Force, is being provided by the evidence-based practice centers of the Agency for Health Care Policy and Research, and at least so far, the quality of the product they are turning out for the U.S. Task Force is extremely good and very helpful.

I think one of the things we need to do is to debate amongst ourselves about whether to make a recommendation for those issues that are difficult enough to come to our panels. We need to have a structured background paper ideally by a group with a track record.

Alan, do you want to respond, as well?

DR. GARBER: Yes, I agree. I think it would be helpful to have some kind of rating of evidence, and there is a fundamental point that I think is implicit in what I said, but is often overlooked by people who aren't familiar with these processes, and that is, the goal of a panel, such as ours, or the individual panels and the Executive Committee, it is not to make the best guess about whether something works, it is to decide whether there is enough evidence to draw conclusions is the first step.

So, there is nothing inconsistent with saying for my loved one, I want them to have this procedure that isn't very well studied yet, it is still investigational, because my hunch is this is the best thing out there, yet, at the same time, saying but the evidence isn't sufficient for a panel like this to conclude that you can draw conclusions about effectiveness.

That is something that in public arenas is often overlooked, that people tend to confuse the two tests. One is what is your best guess, and the other is do you have enough evidence with the fairly structured process to draw conclusions.

I think the farther we go toward having ratings of the types of evidence, the better we will be. Now, that does put heavy demands on staff, and I completely agree with Hal's comment that that is a recommendation we might make, that staff should prepare reports that include evidence tables ratings for the types of evidence, and also summarize what the evidence shows.

DR. SOX: Dr. Murray.

DR. MURRAY: I would like to ask Dr. Garber to comment, and I could equally well have asked Dr. Burke or several other speakers this morning, because it is the same concern that I have, and that is, that there seems to be a focus on a specific level of evidence that there is something out there that reaches the--I think it was Ron Milhorn that said how much evidence do we need, and the answer is enough.

Well, identifying enough is, of course, very, very difficult, but what I would like to ask Dr. Garber is, is it reasonable or is it within the framework of the way this panel operates that the recommendation that is ultimately framed and voted upon must be consistent with the level of evidence, so if there is strong evidence, then, that should result in a strong recommendation.

If there is evidence of moderate strength, that should result in a recommendation of a moderate level or a more vaguely worded recommendation, and so on.

Are we looking only for strongly worded recommendations or should we frame the recommendation that is ultimately agreed upon to correspond to the level of evidence?

DR. GARBER: Well, I would be happy to take a stab at that, but I think that is really a question for HCFA, and I think it is a very good question. In fact, there is precedent for both the kind of gradated recommendations that you are bringing up as an option, and for the sort of binary recommendation, an either/or decision.

As I understand how coverage decisions usually work, it is either/or with the exception that you can define specific situations where there are exemptions. For example, this procedure is covered only if it's done in a so-called center of excellence, or it's only done in this particular patient population.

The U.S. Preventive Services Task Force--and Hal could comment on this more--has taken the approach--now they are basically developing guidelines--of giving the gradated recommendations that you mentioned. That is to say, when there is strong evidence of high benefit, you make a strong recommendation. When the evidence is weak or there is strong evidence of only mild benefit, you might make a less strong recommendation.

But the real answer to your question has to come from HCFA, that is, what kind of advice would they find useful coming from us, and I would suspect they don't want vagueness, they want a precise statement of what the data show and what our recommendations are and the reasons for the recommendations, and if the data are equivocal, we say we cannot make a strong recommendation because the data are equivocal, and so on.

I don't think it serves anyone to make a vague recommendation, but we can make a recommendation that clearly states either there is or is not enough evidence to make a strong recommendation, and these are the reasons for our decision. Hal, maybe you can--

DR. SOX: Actually, I was going to ask Hugh to respond.

DR. HILL: We are a work in progress on this, as you know. We would appreciate, I think I can say safely at this point, confidence intervals or some kind of an indication of how firm you are in the recommendation.

That is consistent with our request for advice. We are not asking you to make the decision for us. We are not abrogating our responsibility to make policy or trying to devolve that to the committee. In fact, we are specifically avoiding that.

We are asking for your advice, and if that advice comes with qualifications, honest qualifications about how you reached that decision and what level of confidence you have in it, that would be very helpful to us.

I think Dr. Garber is right about both the gradations and the sufficiency threshold, not the sufficiency of whether or not we should cover, but the sufficiency of the evidence for saying whether or not you can say that this service or product is effective.

MS. RICHNER: And that is based on what criteria, on the criteria that Ron Milhorn suggested this morning, or is the criteria to be decided here today in terms of what are we looking at, strong, medium, or weak evidence, and how do we determine that?

Once again, I think we have to remember that there is a process going on, in place right now in your agency, on determining those levels of evidence. How do we do this?

DR. HILL: We are hoping that you will share with us what you think is an appropriate level for saying something is medically effective. As a clinician, as a therapist, I will offer a patient something if I think it is effective, and I have to arrive at my own conclusions about whether or not there is sufficient evidence to say that or not, so, too, must you all in this process and in your professional lives.

If you can over and above that say I believe this evidence to be better or worse than this other kind of evidence, that is helpful, as well.

MS. RICHNER: We use then Dr. Garber's suggestion of those two questions in determining our level of evidence and whether it is acceptable.

DR. HILL: I think I would have to ask him to restate the questions before I answered that one.

DR. GARBER: Well, the first was basically to decide whether the evidence was adequate to draw conclusions about effectiveness, and then the second was really does the whatever it is we are investigating, the intervention, improve health outcomes, but I left as a question for discussion relative to what, and I think--

MS. RICHNER: Relative to what is critical.

DR. GARBER: That is critical, right, and that is not something that I want to make, and I think that is what we need to discuss as a committee.

DR. FERGUSON: To some extent the debate in both of the committees that I have seen, ours last month and Dr. Holohan's committee the month before, was framed by the questions that HCFA asked, and I think that that is a very important aspect of this thing because what questions are asked and how they are asked was really framing the debate.

I am not certain that the best questions were asked or even asked in the best way.

DR. SOX: Dave.

DR. EDDY: Let's see, we have I think four planes stacked up in the air now waiting to land. I would like to make a quick comment to Dr. Francis' suggestion that we have a formal workup. I think Alan spoke to this.

I would like to also endorse the idea that a formal workup, a description of the evidence should be performed, I will add for every question, so that each committee member is looking at the same thing

and doesn't have to fight through the articles in the stacks and things like that. That is thing one.

Thing two was just brought up, which--

DR. BROOK: David, is it appropriate for us actually to make a decision about that at this point, that a state-of-the-art mechanism be used to put together the evidence, so that we are clear that from everything from a literature review, gathering the emphasis, the synthesis of the evidence, the putting it together, that it meets standard scientific criteria for putting together the evidence and answer each question, and that that document then becomes a document that is part of the public record?

I have a conflict with that, because I am one of the organizations that produces such things, as most of the panel is here, so I would suspect we are all--I mean somebody mentioned academics have conflicts--we are all in conflict about that recommendation, but the bias would be that at least the evidence ought to be assembled in a scientifically rigorous thing that is unassailable from the standpoint that it was comprehensive, it was organized, it presented the information, and that no panel should meet until that information is put together in that way?

DR. SOX: I think we will get to a vote on something like that at some point.

DR. BROOK: I just wondered if we could do that, if we could separate some of these planes and solve some of them in the morning and solve some of them in the afternoon.

DR. SOX: I want to consult with Sharon and Hugh because we have to be sure that we have a process that fits sort of the criteria for open meeting and opportunity for informed commentary, and so forth, so that whatever we come up with is not going to be subject to challenge later on.

In other words, I am saying I think we can get there, but I am not sure whether the process would be to take a vote right now as opposed to either a vote later today or possibly a vote after we put together a plan that includes that as part of the process.

So, we will get to a vote on something like that. I can't say whether it is going to be now, later today, or possibly at the beginning of the next meeting, after there has been a chance for public commentary.

DR. BROOK: I am going to argue that we ought to give HCFA technical advice that no panel be conducted until such information be put together, and that this process should be delayed until such a process can be put together in terms of that when I looked at that material, if I was a panel member of that process, I am not worried about all the secondary questions that were discussed this morning, it would be impossible for me as a panel member to understand what the state of the evidence was on a technical level, let alone to worry about whether I needed randomized trials or other kinds of trials, and that is inadequate for making these kinds of decisions that affect people's lives.

I just think in a constructive way we ought to move--if we could move that agenda faster, because you

have all these committees backed up, and I don't really want this process challenged on the basis that not only is it legally wrong, or policywise wrong, but that you get all the scientific people to get up, as you just sort of did nicely, to say that in other processes that have been conducted, the information has been put together in a better way. I mean I don't want other of our colleagues getting up and saying that therefore, this process really is something that we would not look very favorably at.

So, I just think before we deal with a stack of claims, this is the premier question at the moment in front of this committee.

DR. SOX: Bob, it would be very appropriate for you to make a motion. I think probably when we come to the voting end of this discussion, rather than now, and Dave, I will let you get back into your comment.

I just want to remind you that we want to hear from John Whyte and then have some more time for discussion, but take off where you left off.

DR. EDDY: So, I think you are getting the sense that we would like to try and get this plane landed and however that should best be done in the context of the meeting, we will do it that way.

My second observation has to do with the questions. I agree with others who have said that I think we have to be very, very careful about how we define these questions, because exactly how they are worded, the order in which they appear, what is there, what isn't there, has a profound effect on the thinking of the committee.

I think, first of all, we should try to come up with like a structured sequence of questions, a template that we would begin with as the default position for each one of the technologies that is going to be assessed, understanding that that template will have to be tailored, but I think we should try, not at this meeting, but at some other, perhaps by the next meeting, to come up with a template of questions and I think I would like to propose that the Chair and Co-Chair be invited to participate in the final structuring of the questions to maximize the chance that the panel does do its work as you expect.

The third plane that I think is still in the air has to do with this idea of levels of evidence, and so forth. I always struggle when I hear about levels of evidence for reasons that other people struggle, as well.

We all know that each one of the types of designs has pros and cons with respect to each one of the types of biases, and no single piece of evidence is best for all purposes.

Therefore, I actually like the way Dr. Hill formulated it, which is what we want to get is from the totality of the evidence, taking the various designs, biases, sizes, and things like that, a sense of the confidence intervals, if you will, the statements that we can make, and the degree of confidence we have about those statements, about the effect of the intervention on a variety of things, in particular the health outcomes.

I would like to propose that we try to operationalize that process as much as possible. I don't think it's anything that we can begin to do in a session today, but I think it should be an assignment to this committee or a subcommittee of this committee to take a shot at trying to come up with an operational set of questions, once again with the goal of achieving some consistency, uniformity, and correctness to our decisions.

The last comment I have is about the question about what the comparison should be when we are evaluating a new technology and we are trying to decide whether it's superior in some sense or equivalent if a question comes up as to relative or compared to what.

I don't know that we can close on this issue today. I would just like to say that I think I at least would like to see two statements. I would like to see a description of how well this technology compares to doing nothing, and I would also like to see a comparison of how well it does to the other available technologies.

I would not omit the first question just because I think in many contexts, the setting, the cost, the logistics, a variety of factors might have us want to do things which aren't quite as good perhaps as an alternative, but there are compelling other reasons that everyone would agree to that would make it worth doing.

I am also worried about the fact that if we say that something must be better than something else out there, it makes whether or not a technology is effective vulnerable to which one came in first.

For example, if streptokinase comes in first, it's clinically beneficial. TPA then comes out, it is clinically beneficial, what happens to streptokinase? Is it no longer clinically beneficial? Obviously, it's still clinically beneficial.

On the other hand, if TPA had come out first, then, streptokinase comes out. If we have a strict rule of superiority, streptokinase would not be beneficial. I just don't like the kinds of inconsistencies and logical fallacies that come from that.

So, I think two statements gets us around that.

DR. SOX: Perhaps it would be good at this point, Alan, do you want to respond to any of the comments that Dave made, and then I think we will go on to hear from John.

DR. GARBER: Briefly. I am very sympathetic to David's suggestions and largely agree to them, but let me point out that the example of streptokinase and TPA is exactly the kind of thing I had in mind when I said clinically, we look for some advantage, and I would say that if streptokinase came out second, and it costs what TPA costs, and TPA costs what streptokinase costs, nobody would be interested in it, and, in fact, streptokinase still confers one advantage in some situations, which is that it is much less costly than TPA.

I realize you are trying to get us out of the box of trying to be explicit about cost, and indeed it may be that HCFA has to ignore whatever we discuss about cost, but, in fact, there isn't much interest in a new intervention that provides absolutely no advantage over what is out there, and, in fact, streptokinase, if it came out second, given its cost, would provide an advantage relative to TPA, but it is all in terms of cost.

DR. EDDY: We agree if cost can be included in an assessment of advantage, so the last recommendation I would like to make is that we get explicit guidance from HCFA about the extent to which we can or cannot, should or should not take cost into account in defining whether something is reasonable and necessary.

MS. RICHNER: Shall I talk now? Costs are not part of our mandate here as far as I know. I think the Executive Committee, our mandate is to operationalize the panel decisions that were done in the past and to essentially validate those decisions, cost is not part of the equation, and I believe that Dr. Kang and others at HCFA are writing a rule now regarding costs, and as I think Brad had mentioned earlier, that that is something that would allow the public to comment on, so I don't think that is part of what we can consider.

Costs are considered in the payment side of the equation, they are not considered in the public side.

DR. FERGUSON: Is that the answer? You may want to table any decision about that for the immediate future.

DR. SOX: Bob.

DR. BROOK: Since we are only advisory, and nothing we do makes any sense anyway, I think we should follow up David's suggestion. We should ask every time we come to an issue, where we believe additional information from HCFA and from the lawyers at HCFA are useful, it is my belief impossible to apply a reasonable criterion to a capitated world without considering cost.

Now, that may be illegal, but we at least ought to advise HCFA that we would like to see a determination of that, and if that has to be debated in the courts for 20 years, and we have no business doing that, that is fine, but it makes no sense to exclude things that will be part of any developed countries assessment of technology and coverage in the next century just because we don't have the information.

I have no information to prove you are right or wrong.

MS. RICHNER: I am not implying that, though, because we have DRG system, we have the ATC system, we have to argue cost effectiveness with those, that with that payment mechanism at HCFA. On the coverage side, that is another issue, we are talking about medical evidence and clinical effectiveness.

We have as a responsibility of the industry, I have to--

DR. BROOK: I am asking for clarification, and you may be right. I am not arguing you are not right. I think we need clarification. I mean we heard at the beginning of this session, we heard that we are an illegal body that should all be, you know, whatever, sent home immediately on the next plane from a lawyer who--you know.

MS. RICHNER: HCFA has the fiduciary responsibility to make these decisions, but it should be we do this--

DR. BROOK: We are a technical advisory body, and I think we have a right to request of HCFA, if we are serving HCFA, information to address that question, and the definition and most of the articles, if you read most of these articles that have been written, including David's article and the article on medical technology, and all these articles, there is not a one of them these days that doesn't use something that looks like money in it.

MS. RICHNER: Right.

DR. BROOK: So, the question is, under this broad rubric of medical technology assessment and reasonable and necessary and effectiveness, this is open for debate, and I would urge that there be some process that informs us about whether that is part that we can instruct or work with or advise HCFA that when they run these other panels, that basically, what are the criteria that ought to be included here.

We do not know at this moment whether we can even advise that there ought to be a structured process. We don't even know at this moment, as far as I can tell, whether we can even advise about whether a randomized trial is better or not than, you know, the physician down the road divining from the astrology community whether or not this things works.

We don't even know whether it is going to be the evidence for something or against something. We have no legal basis here, and we need some clarification for the panel because that has been challenged.

MS. LAPPALAINEN: I would like to remind my panelists, and you can tell this to all of the members of the Medicare Coverage Advisory Committee, you are quite legal. We have a legal charter signed by the Secretary of the Department of Health and Human Services.

It was signed under the auspices of the Federal Advisory Committee Act, an act that was signed into law in 1972. You are chartered and authorized underneath that charter which describes your function, and what you are doing today is stated underneath that charter.

DR. SOX: Well, that's a relief.

DR. BROOK: I would like to go on record in supporting that we do not foreclose the cost issue simply

because the presentation to the panel said that we can't do it, and that we basically ask HCFA to make a determination on this.

DR. SOX: I think it's reasonable for us as citizens to challenge system. That is what you are saying.

Let's at this point move on. John Whyte from HCFA is going to give a presentation on evaluation of new technologies.

HCFA Presentation - Evaluation of New Technologies

John Whyte, M.D., M.P.H.

DR. WHYTE: Thank you, Dr. Sox.

[Slide.]

As you can see by the schedule, I have 15 minutes to talk about how HCFA evaluates new technology, and that is not a lot of time even for someone like me who can talk fast. So, HCFA can tell me I have had my 15 minutes of fame, and therefore, perhaps be quiet in the future.

[Slide.]

The first thing I want to do with the first few minutes is to thank all of you for participating in this process, and it is very much a partnership and we appreciate your involvement.

As I look around this table, I am most impressed by the people that we have assembled here. It is very difficult to pick up an article or a book about health services research and evidence-based practice, and not read about or see reference to Dr. David Eddy or Dr. Alan Garber or Dr. Hal Sox, or to read about quality of care, and not see references to Dr. Bob Brook, and I could go on and on about all the panel members, but it is truly an honor to have all of you participate in this process, and I think the richness of the past discussion is a testament to that.

In any partnership, hopefully, there is a mutual benefit.

[Slide.]

You might be thinking that here is HCFA again asking for more and more, we want more advice, we want to have more meetings, but hopefully, you will realize that we are excited about this new process, and you can have a tremendous impact on how we improve the process and improve access to new technologies.

[Slide.]

I don't know if you can read that, but there are several points on it, it is just a hunch, but I think we could improve the process, and that is what we are trying to do, to improve the coverage process.

[Slide.]

Just to remind you this actually is the process. I don't expect you to read it, but just to remind you of that, and I think you start to realize when you have been in government too long--and I have only been at HCFA for about a year and a half--and you see flow charts like that, and you think, well, that is pretty simplistic and unencumbered, so if you think that is simple, then, perhaps you should work with us.

[Slide.]

Now, we have heard a lot this morning about evidence-based medicine and everyone uses the term "evidence-based medicine," often inappropriately, and really today's discussion is to engage in a dialogue about how we should make coverage decisions. It is to collect views from the various stakeholders in this process to help shape our thinking.

Now, in the remaining 10 minutes, I am not going to have the ability to spell out how we should make coverage decisions, but again, it is to provide food for thought and to encourage the dialogue that has begun.

Now, sometimes it is easy to say what evidence-based medicine is not.

[Slide.]

I don't think this would exactly count as peer reviewed, but it points out about how cures found in space, wipe out all diseases, or superhealing power of lemon juice, so it is difficult to exactly figure out where does evidence lie.

Now, many of you know John Eisenberg, who is the Administrator of the Agency for Health Care Policy and Research, which this week changed its name to the Agency for Health Care Research and Quality.

Now, Dr. Eisenberg is my concept of Renaissance Man. If you go to any of his talks, he will quote Shakespeare, he will quote Dickens, and authors from all of these books that I guess we were supposed to read in high school, which Dr. Eisenberg apparently has.

In my attempt to be a Renaissance Man, I looked for a quote that I thought would be pretentious enough and appropriate for this discussion, so if I could have the next slide.

[Slide.]

It is by Alfred Lord Tennyson and it is "Science moves, but slowly, slowly, creeping on from point to point."

[Slide.]

Some people might change that to "HCFA moves, but slowly, slowly, creeping on from point to point," and I wrote Anonymous, although I could attribute that to many people, I am sure, in the audience.

But the point is when Tennyson made the quote, it was the 19th century, and since then, there has really been an explosion of technology.

We have technologies today that were not even dreamed of just five years ago, and it's an exciting time to be at HCFA and to learn about new technologies. As a physician, my physician colleagues will often ask me or are surprised why I work at HCFA, but in many ways, as a provider, clinician, or physician, whichever term you want to use, to be involved in the process is exciting. You have the best of both worlds.

You get to see individual patients and, at the same time, talk about access of technologies to broad populations, and there is not many opportunities for you to do that.

The challenge for the agency is to determine when there is sufficient evidence to cover a new technology, so what I thought I would do in the time that I have is take you through a few examples.

[Slide.]

The first example that I want to use is cardiac MR. Many of you have been involved with ultrafast CT through the Blue Cross/Blue Shield tech, but I am going to talk a little bit about a new technology, cardiac MRI.

There is only about 20 centers in the world that use cardiac MRI in the diagnosis of cardiac disease, although it is expected to increase significantly over the next few years. Essentially, cardiac MR is a type of movie capturing motion of the heart as it contracts and relaxes during systole and diastole, and the images are taken continuously during the beating motion of the heart, and it thereby detects abnormalities of the heart.

So, for each point during the cardiac cycle, a scan can capture data about blood flow including location, quantity, and speed of blood cells, so for all you physics majors, you know that is a vector. Basically these vectors are represented by color scheme that you see in front of you.

These colors represent different amounts of wall thickening and plot a funnel and it represents either

systole or diastole. That may sound very complicated, but it really isn't.

If you remember the colors represent vectors, and it is somewhat arbitrary which color is normal and abnormal, but if I told you yellow was the fastest color, you would say that is likely the apex of the heart, and red is normal, and blue represents abnormal speed and abnormal thickness.

So, here, what we would have is essentially, if I told you that was an area from the left ventricle, it is pretty easy to see you have a blue area that represents abnormal tissue, and that represents an infarct in the left ventricle.

So, again it really isn't that complicated. If we look at the next picture, here we have a concentric area of blue, which I have already indicated to you is abnormal tissue, and a small area of red.

[Slide.]

So, we have a concentric area of heart wall thickening, which is consistent with congestive heart failure. So, it is pretty easy to tell, and what is interesting or maybe even fascinating is that it is a huge difference from ultrafast CT. In CT, you essentially have one spatial orientation, in MRI, you have an infinite number of orientations.

[Slide.]

Anyone could look at this and see essentially what is called an oblique sagittal view. You have a lumen, and you have narrowing, and you would say this must not be good, it doesn't look right.

[Slide.]

This is typically what you would think about in cardiac MR. You have the region of the heart. I could actually point out some blood vessels that. The interesting part is that cardiac MR can distinguish between soft, cheeselike atherosclerotic plaques, which are often likely to rupture and release thrombi, as opposed to the firm or more solid plaques which are less risky, and there is not a lot of present technologies that allow us to do that, and it's non-invasive, so why not cover it, what's the drawback to covering it?

Randel, do you have any thoughts? It is meant just to be rhetorical, so I don't expect you to answer.

If we could have the next slide for another example.

[Slide.]

A colonoscopy. I am sure that many of you would say, you know, who wouldn't drag drinking a gallon

of Go Lightly and having a tube with a light inserted into an area of your body, if you didn't have to undergo that, who wouldn't.

So, the question is, is there an alternative? Maybe there is.

[Slide.]

There is now virtual colonoscopy.

[Slide.]

This is essentially a spiral CT to obtain a sequence of two-dimensional images that are then translated into a 3-D volume, and then a computer program can visualize it with various software.

[Slide.]

So, what you have here is essentially a cross-section. The blue represents a polyp, pretty easy to tell.

[Slide.]

Typically, after colonoscopy or flex sig, you give patients pictures or you put it in the medical chart, and here you can see through scanning the entire colon, you have various polyps there, and you can make certain decisions about that.

[Slide.]

In contrast, what you have in the lab is the typical visualization that you have on colonoscopy. Again, on the right, you have the representation of the polyp, and it's non-invasive, but is there data out there, is there sufficient data.

[Slide.]

What about fructosamine monitors? Everyone has heard about glycosylated hemoglobin, but what about these fructosamine monitors? Essentially, it reflects blood glucose during the past three weeks. For some patients that may be having abnormal glucose levels, could this be useful, but is there a problem with that? What is the standard?

If fructosamine monitors came out first, would that have been the standard as opposed to the convention is looking at a glycosylated hemoglobin, so what is the role of the fructosamine monitor? How much data do you need?

So, again, for all these examples, whether it is cardiac MR, whether it's a virtual colonoscopy, whether it's fructosamine monitors, which are all real examples, how do we evaluate them?

[Slide.]

What do we look for?

First, we want to see that something is safe.

[Slide.]

Next, we want to see that it is effective. Remember, those are done by the FDA. Their language is safe and effective.

[Slide.]

We would like to see that benefits outweigh risks.

[Slide.]

We would like to see evidence of improved outcomes.

[Slide.]

We would like to see added value.

I believe in giving appropriate attribution, and I am very proud of this slide, which stacks things up, and I can't take credit for it. Bonnie Patell, who is in the audience, actually made this very nice slide.

[Slide.]

What you will notice that is not in there is the issue of cost, and several people have brought up costs in this morning's discussion.

[Slide.]

So, what about costs?

[Slide.]

We have opportunity costs.

[Slide.]

We also have additive costs.

[Slide.]

I am going to read a quote from an article that was published in JAMA a few years ago, and it is actually a quote from one of the panel members, and I won't say yet who the panel member is.

It says, "As a society, we should and do encourage innovative technologies for health care. However, these innovations must be thoroughly tested and evaluated before we as a society can pay for them."

[Slide.]

"By legitimizing insurance coverage of inadequately examined, questionable, unsafe, or ineffective medical procedures, we encourage the use of these technologies by other providers and consumers in the future, possibly as substitutes for more effective technologies."

I don't know if Dr. Ferguson remembers that--

[Slide.]

That was actually written by Dr. Ferguson in a discussion--the actual discussion was on court-ordered coverage, but it's an important point, and it's something that I want to talk about in terms of in opportunity costs, which several people have really overlooked.

The issue is people will often come to us and say, well, why not cover it, why not give people the opportunity to have access to this new benefit or to this new procedure.

The difficulty is that coverage by the Medicare program in many ways legitimizes procedures. It gives some equivalent benefit or the perception of equivalent benefit. So, there is a real danger in approving technologies too early.

For instance, we presently don't cover stem cell transplantation for breast cancer. Many would argue that the data is murky. The difficulty is if were to quit in covering something, does the public perceive that as equivalent benefit, and by perceiving it as such, forego more standard therapy even if that standard therapy has minimal benefit, if it's better than no benefit, and it's presently the standard, shouldn't patients have access to that.

So, I think that is an important discussion. I think that is something that people have to think more about,

because there are opportunity costs associated with coverage of new technologies, and it is primarily in the field of foregoing perhaps the more standard benefit.

[Slide.]

There is also the issue of additive cost, and often what you will find is that services don't often replace one another, sometimes they become duplicative, and that can be depending upon the time that they enter the professional community.

In my own example, I am an internist by training, but have worked in a lot of ER's. What you will see is that patients will come with some type of neurological deficit, they will have a CT because you can order that relatively quickly in the emergency room nowadays, and then the neurologists will come down and they will say, no, you shouldn't have ordered a CT, you should have ordered an MRI.

So, the issue becomes how much added value does a new technology provide, is it merely going to be duplicative, or is this new technology still not well accepted, and you could go back to the fructosamine monitor, as well. Are people going to get a fructosamine level and still get a glycosylated hemoglobin, so what additional value is going to bring? Some of that relates again to the time that it enters the professional community.

[Slide.]

So how do we do it? Unfortunately, I don't have more time to talk about it, but that really is the purpose of today's discussion - how do we make such decisions, and we are really asking all of you for guidance to engage in the rich dialogue that you have started.

[Slide.]

The one message that I want to leave with all of you is to address the perception that at times HCFA is a brick wall or it's an obstacle to new technologies, and that perception is truly an unfair perception.

[Slide.]

I couldn't think of the right image to use, and my Power Point is limited, but the image that I chose was a doorway, and it's not closed, it's not fully open, it's slightly ajar, and perhaps that is a good image because what we are trying to do is to cover things that are medically necessary and reasonable.

We want to improve the lives of beneficiaries, we want to increase access to new technologies. We want to do the right thing, but there is also an awareness that there are opportunity costs associated with covering new technologies, and that is what I would encourage all of you to entertain in your discussion, that too often there is again the perception why not just cover this, why not let patients decide.

Again, I thank all of you for participating in this process, and personally, I look forward to working with all of you.

Thank you.

DR. SOX: Thank you, John.

Open Committee Deliberation

DR. SOX: It is now about 11:25 and we will be breaking for lunch at noon. We will have 15 minutes for public comment about the morning's discussion. We will come back at 1 o'clock and have about 1:30 to decide what we are going to recommend happen between now and our next meeting to try to provide guidance for the committees. So, that doesn't leave us a lot of time.

After that, we are going to have a discussion of two proposals from our panels, and I think those are going to generate a lot of discussion, as well.

So, I think it is going to be important for us to stay on point here and on time.

At this point, I think we ought to start talking about what kind of recommendations we want to make relevant to providing the panels with as much useful information as we can about how they should proceed during their deliberations that will be coming up in the next months.

Linda.

DR. BERGTHOLD: Well, I would like to start with just a simple suggestion. I can't make a motion, but I don't think it needs one.

DR. SOX: At some point we are going to need a motion.

DR. BERGTHOLD: Okay. Someone can. That is, that we provide all of the participants of the impaneled folks in all six panels with a set of materials out of what we do today, and I assume we were going to do that anyway, but one of the things I think we really should be sending out to folks, and soon, so they don't get it all at once, would be Dr. Garber's paper on Evidence and perhaps the IOM article, so that everyone starts on the same page.

When I sat in on the first panel that we did back in September, and there was really no--I mean I went and talked to some colleagues to explain to me what levels of evidence were, so that I could participate, but I don't think, I don't know that all the panelists came in with the same knowledge about even what the terms meant.

So, even though we have had an orientation, I still think that when you come to serve on a panel, you need a refresher, so I would like to suggest that we provide all the folks that are on panels now, and will be serving this year, at least with some set of materials out of today, and I will leave it to the staff to decide what that would be. At least for consumers particularly, it is quite difficult to understand some of this.

DR. SOX: Linda, as a consumer representative, can't make a motion, which I had forgotten, but I think the sense of her suggestion, which is that we discuss what we can provide the panels now that will help them while we are doing something more definitive to help them would be very useful.

Personally, I don't see this community crafting on the fly a series of recommendations of the panels about how to evaluate the evidence, and that is something I think is going to happen between now and our next meeting, but at the same time, between now and our next meeting, panels are going to be moving forward and we have either got to throw a gear in the wrench and say they can't move forward, which may not be realistic, or we have got to provide them with the best information we can to help them make good recommendations that reflect the evidence while we do a better job of providing them with that guidance over the course of the next couple of months.

So, let's focus on what we can do now to help the panels while we are trying to come up with something better and perhaps more structured and more thoughtful than we can do on the fly.

One possibility, as Linda suggested, would be to say we suggest that you read Alan's article. We think it represents a good outline of the way you should be thinking during your deliberations, at least perhaps to essentially endorse Alan's article as something that they ought to read and try as much as possible to incorporate into their ideas.

Bob, you may have some other ideas about how we should proceed between now and then, but let's proceed to a discussion of that, hopefully, leading to a motion.

Bob.

DR. BROOK: I move that we advise HCFA to develop a web-based training package for panel members that would cover the principles of evidence, and that we encourage the panelists, before they go to meetings--that would include pre- and post-tests--and allow people to understand something about where they know in this process as the long-term issue, and that if we are really committed to an open process, and that anybody could assess this, that this would be a tool that since it is a public process, then not only panelists could, but presenters who might present to us might want to see how they do at this, as well, but that a web-based set of training materials be developed that would include all the principles of education for people who are going to participate in this process.

DR. SOX: So, tutorial and self-assessment, something like that?

DR. BROOK: Tutorial and self-assessment, and I don't know whether any of the specialty societies or others have tried to do that, but that would have to be general enough to allow people who come into this from very different walks of life to learn and be knowledgeable, and that this ought to be done, and I think that's the first thing, because I do believe that people need to be prepared to engage in this process, and that we ought to try to make a constructive step forward in this regard.

I don't think that has to hold up the panel process to do that, but I think that that would be--but we should advise HCFA that that is doable within a year, and not a decade if funding to make that happen could occur.

I would also urge that we either adopt a standard approach that is already being used, such as for the preventive panels, or the U.S. Preventive Task Force approach or that is being used by agency--evidence-based about what are the standards of putting evidence together for the panels, so that at least there would be a structured paper and process put in front of the panel.

Now, we could debate whether we want to hold up the process until that is done, but that we ought to recommend--and I don't know whether we can do this without seeing all of the different versions that are now floating around--but the technical advice would be that somebody at HCFA examine what is out there and what is available for this structured process, and then comes back either to this committee at the next meeting about what are the options here in terms of doing it, and we could give them advice about which one. Again, this is not policy, we are giving them technical advice about which way would you put and organize the evidence together, what kind of a document are we looking for.

DR. SOX: Those are two motions. We can't have a discussion without a second. Actually, let's discuss one at a time. Why don't we take the first one first, a second to the first motion?

DR. FRANCIS: Second.

DR. SOX: Let's have a discussion of Bob's proposal that HCFA develop a web-based I guess tutorial on evaluation of the evidence, that we would strongly urge any member of the panel to take that, to go through a self-assessment.

Basically, the idea is try to bring everybody up to speed on the principles of the evaluation of evidence, so we are all talking on the same page when we get into those panel meetings.

Any discussion? Tom.

DR. HOLOHAN: As part of your motion, would you agree that this could be contracted by HCFA to another organization?

DR. BROOK: What I mean by that, I don't have any sense of how--I mean it could be--

DR. HOLOHAN: So, it doesn't matter, and if they went to AHCPR or contracted with the National Health Service's center for Research and Dissemination, it wouldn't make any difference.

DR. BERGTHOLD: They could also just put articles like Alan's thing on the web site tomorrow.

DR. BROOK: That's another attempt. My belief in this day and age, I mean I would argue that that is not sufficient. People don't read articles, reading two or three articles when they are redundant, that could be put together in a more efficient way.

What we are learning with web-based training is that you can achieve the same learning objectives, but you do it in about maybe 40 percent less time. I mean people's time is valuable. We heard the story about nobody is getting paid for a colonoscopy, and therefore, they only look at 1 centimeter beyond the sigmoidoscopy. It is hard to believe, but I will accept that as my physician peers do these kinds of things these days, but if that is true, then, at least for the people participating in this process, we ought to agree that they might also be motivated similarly.

DR. SOX: Other discussion of Bob's motion? Daisy.

DR. ALFORD-SMITH: I guess mine is probably more of a question than it is a statement. It would probably speak to any of the issues that we are attempting to address.

DR. SOX: Excuse me. Could you use the microphone, I am sorry, we want to hear every word. I am having a little trouble hearing you.

DR. ALFORD-SMITH: Sorry about that. I am just really attempting to clarify--I am going back to what our intent is--I recognize what we need to do as it relates to the evidence, the scientific advice, but I am also trying to attempt to incorporate our second role, which I read as encouraging some type of public interaction or interfacing with the public.

So, to what extent do we take the response or the sentiment of the public and use that as part of some type of information which could support again or be at least assessed along with the evidence-based information that we are to receive?

DR. SOX: As I understand it, you want to have some mechanism whereby public opinion about a technology would have input into the panel's deliberations? Did I hear you correctly?

DR. ALFORD-SMITH: Yes. Well, the way I read our role, I mean it does speak to this part of that. So, I would hope that we would not overlook that aspect of it.

DR. SOX: Are you suggesting that since we are discussing the specific motion, that the content of that would reflect some effort to take into account input of public opinion and thinking, is that what you are getting at?

DR. ALFORD-SMITH: That's exactly it.

DR. SOX: Okay. I think that sounds like a friendly amendment.

Ron.

DR. DAVIS: I like the concept behind the web-based tutorial, but I have two concerns about it. One is I think we are getting a little bit ahead of ourselves and first we have to decide whether we want some sort of formal structure for this decisionmaking process that we are all going to have to go through, panel by panel, and then we are going to have to develop that protocol, and then we will know how to structure a tutorial for the panel members.

So, I think the order is a little bit off, and if people agree, maybe we could just table this motion until we deal with some of the other ones that might come earlier.

The other concern is even if we get to that point, how quickly could the tutorial be put together, could it be put together to impinge on this process quickly enough, so that we don't hold up the panelists, and if it can't be done right away, maybe it would be a tutorial that is not web based initially, but then becomes more sophisticated and more modern over the next year or two.

DR. SOX: So, are you making a motion to table until we have considered the issue of whether to have a structured approach to the evidence in the first place?

DR. DAVIS: Well, that makes sense to me. I was looking to see if I saw some nodding heads, but I can offer the motion to table that until we deal with some of these other matters, but if people disagree, then, I guess we can vote down that motion.

DR. SOX: David, do you have a comment?

DR. EDDY: I mean I think it's a fair question. We did skip beyond it, so let's do it, and you can decide which order to do these things in, but I will make a motion that a task of this committee is to offer advice to HCFA on a formal structure and a formal set of processes and definitions for the panels making their deliberations regarding the technologies.

DR. SOX: You can't make that motion until we deal with the current one. That is what Robert Rules of Order are about, try to help us to get confused.

So, if I could hear a second to a motion to table?

[Second.]

DR. SOX: All in favor raise your hand.

[Show of hands.]

DR. SOX: So, now we have tabled that motion, we are in a position to consider Dr. Eddy's motion, but Sharon is whispering in my ear.

MS. LAPPALAINEN: A count of show of hands? We had a second to the motion. We need a show of hands again, please.

[Show of hands.]

DR. SOX: It's the motion to table.

MS. LAPPALAINEN: Is it unanimous?

DR. BROOK: No, I am opposed.

MS. LAPPALAINEN: We have one opposed? Three opposed.

DR. SOX: It still carries.

DR. HILL: Hal, did Bob make a second motion right after his first one? I wonder if you need to go to that one next.

DR. BROOK: It's the same.

DR. SOX: Is the same as Dave Eddy's, I think.

DR. BROOK: But I didn't give it in terms of advice. I think we already are in that business. I think your motion is what the mandate of this--as least as I read this mandate--we were supposed to give advice to do this.

What I am suggesting is that we say that we believe that there needs to be a structured process by which the evidence is put together. We can deal with the group process, but we can start from scratch one, that there needs to be a structured process by which these committees meet, and the first part of those deals with structuring the evidence.

DR. HILL: I understand that you have taken that as a motion and we are proceeding based on the earlier second, or do you want another second to that as a motion? It is distinguishable from the one that was tabled.

DR. SOX: I think that Bob's motion was a formal motion, is that correct?

DR. BROOK: Yes, but I withdraw it. I think we ought to try to work together to figure out what this motion we really want is, so we can just sort of work out some language maybe and then do a motion instead of going through formal amendments. Can we do that legally?

DR. HILL: There is a bit of information that we would like to get out to share with you about what we are doing in terms of working towards, at this point, structuring evidence, and if it's in order to talk for two minutes about that now, perhaps it would help you with your further deliberations.

DR. SOX: Yes, it is.

Bob, you have offered to allow Dave to sort of start today's motion to take precedent, and then we can work on structuring that, if that is agreeable.

Why don't you rephrase your motion, Dave, and then we can get a second, and then we can have discussions starting with you.

DR. EDDY: I don't think this is a big deal. I think we all assume it, but why don't we just clean up the loose ends.

So, my proposal would be that we do try to, I am going to say, develop advice on a formal structure and process by which the panels would make their deliberations.

[Second.]

DR. SOX: I hear a second, so now that motion is open, that we, the committee, develop a process or recommend to HCFA that they develop a--

DR. EDDY: Well, I need some help here. I am assuming that we don't have any formal authority at all. We can offer advice to HCFA. We are an advisory committee. So, that is why I structured it as offering advice to HCFA.

Whatever form HCFA wants it in, that is the terminology I want.

DR. SOX: Specifically, if we wanted, we could develop a recommendation for HCFA that could be pretty detailed.

DR. EDDY: Yes, absolutely.

DR. SOX: So, we have a second.

DR. BROOK: You only can do that, Hal, if we have staff and money to do that, and my understanding is that we don't. So, the question is we really have to advise HCFA to do it under these parameters that come back in an advice relationship, don't we? We are not an organization that is going to have staff working for us, or are we?

DR. ALFORD-SMITH: Why don't we hear what they already have underway.

DR. HILL: If I may defer to John, he is prepared to talk about that for a couple of minutes.

DR. WHYTE: It is really just a point of information, and I think we understand your position, and what we have done for the first two committees isn't the approach that we are using in the future for our upcoming meetings, such as the advisory panel on incontinence, and hopefully, you will all be agreeable to what we would like to do, and in some ways perhaps we need the opportunity to see how it is going.

But what we are presently doing is creating a structured review in a grid type format on an access database, and what we are including in that structured literature review is obviously the author, the year of publication, which sometimes is relevant, the type of study design, whether it was prospective, randomized, retrospective, case series, whatever type of study it was.

We also abstract patient characteristics, how many patients were there, what were their ages especially relevant to the Medicare population, how many patients enrolled in the study, how many patients finished, and we make notations if such data is absent.

We also look at patient outcomes, what were the outcome measures, and we specifically list them, and then we also have a section for results, and what are trying to do in there is to add the p values if the author has included it, and if it is not included, we also mention that there is no p value.

So, for those first couple of columns, we are simply abstracting the data from the data. Obviously, not all studies say the type of study, whether it is prospective, randomized or whatever. So, in that area, we have to make a determination what type of study it was.

The final column is a section we are calling HCFA comment. In that section, we are trying to list what are some of the questions that we are asking about this study or what was our interpretation of the study because, as part of an open, inclusive process, we want you to know what our thought process is. So, if you disagree with it, great; at least you know where we are to begin with to disagree.

So we may talk about the durability of results. If it was a three-week study, can we generalize that finding to ten years or extrapolate. If it was only done on a young population, which a lot of orthopedic procedures are, is that generalizable.

So we raise questions. We raise questions about their power calculation, perhaps the lack of statistical data, essentially, what questions we have from the study and how we interpret it. Hopefully, that type of structured literature review, at least as a first blush, provides the type of data that you need. We don't want to provide too much opinion and too much editorialization.

I appreciate your comments about background papers, but it still is a new process and we are trying to find what is the right way. Hopefully, the information I have just provided you gives you much of the information that you would want.

Thank you.

DR. SOX: So let's go back to a discussion of the motion that the Executive Committee develop recommendations for HCFA on a structured evaluation of the evidence which HCFA can listen to or not as they see fit. But we can at least give them the best advice we have based on the experience that many of us have had.

Does anybody else want to discuss that?

DR. GARBER: I just have a question for David about the sense of how this motion works. It is the idea that we would vote on the sentiment but then work with staff to make this more specific sometime in the near future rather than getting the wording down today? What was your intent?

DR. EDDY: My intent was just to get things going. It occurs to me, and I might be slowing things down, that there was some question about whether this committee wanted to get into the business of offering formal advice on a structured process at all. I was just trying to get a quick yes to that.

But my interest is broader than just a formal review of the evidence. It is a formal process with definitions, criteria and so forth. Now, if we answer yes to this, my intent, at least with the motion, and others might be able to improve the terminology of the motion to achieve this, that we are then free to do as much or as little as we want, that this would just ask whether we, as a committee, do agree that we want to try to begin to discuss these things.

DR. PAPATHEOFANIS: What if the answer is no?

DR. EDDY: That is a very important answer. Then I guess the next question would be what is the role of the committee.

DR. SOX: What are we doing here?

DR. DAVIS: Initially, I was going to wait and let this motion be approved before making my next comment, but maybe this comment will impinge on people's thinking right now and that is, okay, if we adopt this motion, how is this going to happen? My thinking was that maybe a subcommittee of this

committee, three or four people in this group who have the most experience and expertise in rating studies and evaluating the quality of evidence, could work with HCFA staff or work amongst themselves and come up with something more detailed, develop that template and then bring that back to the full Executive Committee.

That is how I potentially saw this unfolding if this first motion passes.

DR. SOX: Fine. I think how we carry this out is something that we can work out consistent with the requirements for this being an open process and so forth.

Is there any more discussion? Linda, I think, if this is a motion, I am afraid--

DR. BERGTHOLD: Can I make a comment?

MS. LAPPALAINEN: Yes; you can make a comment.

DR. SOX: You can? Okay; good. Just wanting to stay legal.

DR. BERGTHOLD: The power of the non-vote. Just from having sat through one of these panels, I know you are going to vote on whether or not the structure is helpful. From having sat on one of the panels, I would really like to tell you that, without structure, it is very difficult. There are a couple of us, now, who have done this and, believe me, it is sort of a nightmare to try to make your way through the process without some kind of structured approach to looking at the evidence and a structured set of questions.

So, just from a public perspective, I think structure will help the public get involved with this a lot better as well as help the panelists.

DR. FRANCIS: The quality of the discussion that we had never focussed on, at least a large percentage of it, never focussed on what the quality of the evidence was. So this is probably an additional recommendation but it is worth, I think, putting in that this needs to be down the pike which is, once we have a structure for just gridding out the evidence, what the focus of the committee discussion ought to be is evaluating the quality and challenging, say, whether a study is put in the right place.

We probably heard ten times how many people get multiple myeloma which has nothing to do with the quality of the evidence.

DR. SOX: Hopefully, the structure that we provide will focus on the evaluation of the evidence and, while giving opportunity for people, through a public-comment process, to say whatever they want to influence us, it will focus us on the evidence.

Is there any more discussion about this very important motion?

MS. LAPPALAINEN: Before Dr. Sox calls for a vote, I would like to read to the public the voting members who are present at the committee today. They are Dr. Thomas Holohan, Dr. Leslie Francis, Dr. John Ferguson, Dr. Robert Murray, Dr. Alan Garber, Dr. Michael Maves, Dr. David Eddy, Dr. Frank Papatheofanis, Dr. Ronald Davis, Dr. Daisy Alford-Smith, Dr. Joe Johnson and Dr. Robert Brook.

Dr. Sox, who is the Chair of the committee, may vote only in the case of a tie, to break the tie vote.

DR. SOX: I would like to call for a vote. First, to restate the motion that we, as a panel, will develop recommendations to HCFA about a structure by which the MCAC can evaluate the evidence before it and that we will make at least a preliminary report but, hopefully, a final report at the time of our next Executive Committee meeting.

DR. GARBER: This is a small point; we as a panel, not we as a committee? The "we" refers to the Executive Committee?

DR. SOX: "We," as an Executive Committee. Thank you.

All in favor, please raise your hand.

[Show of hands.]

DR. SOX: Any opposed?

[No response.]

DR. SOX: The motion passes.

Open Public Comment

At this point, I think we should go back to our agenda which calls for the opportunity for open public comment. I would remind anyone who wishes to speak that they come up to the microphone and that they state that whether or not they have any financial involvement with manufacturers of any products being discussed or with their competitors.

So this is an opportunity for anybody in the audience to comment about anything that they have heard during the last several hours. Encouragement would be appreciated, but we will take anything we can get.

DR. BURKEN: I am Dr. Mitch Burken. I am a medical officer with the Coverage and Analysis Group at HCFA. I have a couple of slides.

[Slide.]

I just want to make a couple of points, I think, that reiterate and summarize some of the discussion from earlier in the day and casts it in a somewhat different light. But, when all is said and done, it is the HCFA staff that really needs to work with this evidence and write coverage policies or assist our carriers in making such decisions since, again, one of the options is to have carrier discretion.

Coverage policies, if we do them ourselves or if the carriers develop the coverage policies, are really driven by the need to be ICD-9 code-specific which means we need to live by the motto, "The devil is in the details." We, at Central Office, don't get terribly involved with coding. Even if we make a national policy, oftentimes, the coding decisions are made at the local level. But, still, our policy making is driven by this need to be very, very specific.

Therefore, broad levels of evidence may not provide the sufficient guidance unless more detailed evaluation criteria are applied.

[Slide.]

I put together another slide, just a little bit of a hypothetical illustration just to show you were I am going with this. Let's just say that, for purposes of discussion only, that we had a technology or treatment X--it really doesn't matter--and there were eight studies pertaining to four diseases, again, just for the purposes of discussion, those eight studies fall into the level II-1 and II-2 from the U.S. Preventative Services Task Force again.

I am sure the panelists are well familiar with these so I just use them for an illustration. We will find, at the staff level, reviewing articles that, let's say, again, just very hypothetically, Disease A has three supporting trials, Disease B with one, Disease C with one, Disease D with three.

They are all different studies and I just put down some miniature vignettes. The point is not what the decision is, not whether we cover Diseases A, B, C and/or D but how we get there.

Thank you.

DR. SOX: Anybody want to comment?

DR. EDDY: Am I to understand, from who you are, that this is a process and a classification scheme currently being used by HCFA?

DR. BURKEN: If we could put the second slide up just to clarify this point. Oh; you have the hard copy. On that diagram, as I mentioned, is a hypothetical example just to demonstrate the point that we need to delve into details as HCFA staffers. This is not a category or evidentiary scheme that is being used.

I only put it up here because I felt the panelists would be somewhat familiar with this particular categorization and it would serve to help with my illustration. So I hope that that clarifies it.

DR. SOX: Thank you.

DR. WEISENTHAL: I hadn't planned on making a comment, but Dr. Burken's slide stimulates me to make a comment. He gave an example of the problems where you have got four different diseases and eight studies which broadly apply to those, but you then kind of break it down study by disease and maybe the data is not as persuasive as if you considered it in an entirety.

This reminds me of Dr. Burke's presentation at the last MCAC meeting when there was a study analyzed in which there were 119 correlations between the results of an assay and the results of patient treatment. Dr. Burke wrote down the data and he said, "What you have here is really eight different diseases and eight different drugs and so it is, actually, a mean of 1.8 correlations per drug/disease."

He said, "That is not good enough. What you really need is to fill out the matrix." You have got an eight-by-eight matrix, and let's say you maybe need twenty correlations in each one. He, then, expressed surprise that we couldn't do that easily.

He said, "Well, you can just use banked frozen tissue from all these cooperative studies." You can't use banked frozen tissue. The cells are dead and you can't study them. So that eight-by-eight becomes very formidable.

But I will tell you that, in my own practice, I test routinely 224 different drugs and combinations in about 200 different tumor diagnoses. So I have got a 224 by 200Êtable. I agree with him intellectually. Let's say that I show clinical correlation adequately in one setting--let' say, chronic lymphocytic leukemia.

Does that prove it for colon cancer or anything else? We know, of course, that it doesn't. But the point is that it becomes just an insurmountable task. Sometimes, you have to use some common sense. You have got to evaluate the entirety of the data which is why I so vehemently oppose leaving out studies which are relevant and, also, not confusing the issue with irrelevant studies.

DR. SOX: Thank you.

We will break for lunch and be back here at 1Êo'clock. Thank you.

[Whereupon, at 12 o'clock p.m., the proceedings were recessed to be resumed at 1 o'clock p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:10 p.m.]

Committee Conclusions: Levels of Evidence

DR. SOX: We have about another half hour to run on the discussion about process. I think we made a crucial decision before the break. But I would like to spend a few minutes, now, if we could sort of brainstorming about what we could now to try to help the panels develop--do the best job possible considering the evidence as they go to work over the next couple of months because, whatever process we end up recommending for the program for the whole, it is going to take a while to get into place.

Meanwhile, what can we do now to try to get everybody singing off the same page. This won't be in the form or Roberts Rules of Order. It will just be an open brainstorming session for HCFA staff to listen and take what they think makes sense.

Do you want to start, Rob?

DR. DAVIS: Sure. Well, one question that I think we might need to answer before we get to that is how are we going to see this process we just talked about before lunch unfold? What kind of timetable do we envision for developing these criteria, this protocol, because if that can be done relatively quickly--say, in two months--then that can be used by the panels.

If it is going to take six months or eight months, then that may change how we can get this to the panels for their use.

DR. SOX: It is a little hard to predict because we don't know what we are going to say. I can imagine that some it would useful right away, some of it might take a while to put into place. For example, if we recommended evidence-based practice centers doing the development of evidence tables, that, clearly, would take a lot longer.

We haven't worked out the process but my thought was I would probably ask a couple of people to work together to draft what they think makes sense and then that we would have a process of revision that would involve all members of the Executive Committee getting to a document that we were all happy about.

And then we would do whatever we need to do with respect to public comment and then discuss it and vote on it at our next meeting.

DR. DAVIS: Good

DR. MAVES: I was going to suggest if any of you have dealt with FDA panels, and I mentioned this to Sharon, there is a very discrete set of rules that each panel has evolved over, obviously, a considerably longer period of time. My reason for mentioning it is not to necessarily duplicate or adopt those, but it

certainly would give us, I think, a leg up and a good starting point and we might be able to generically devise a standard operating procedure, if you will, each panel, depending upon the kind of topics they are going to need to discuss.

Medical-surgical will be much different than Devices and Drugs and some of the other kinds of panels around here. So that might be one way to jump-start this mechanism and yet provide us with some standard procedure that I think most individuals in this area have dealt with, either directly or peripherally.

DR. SOX: So being able to get their procedure manuals would be good input into whatever we develop.

DR. MAVES: I think it would be. It would be a good start.

DR. ALFORD-SMITH: I just, again, would like to emphasize what I feel is important and that is in reference to, perhaps, having some understanding of the evolution of the issue--in other words, why it is being referred to the panels in the beginning--because I recognize that we are not receiving all of them. So there is, obviously, a reason for that determination to go to the panel.

It might just add some additional information in our decision-making process as well as what I have already mentioned and that is regarding how--and I am not sure how--this can be done, but some information relating to who the public is and how would should weigh that information, if there is a way that there could be some recommendations for that.

DR. SOX: Other suggestions in brainstorming mode here?

DR. FRANCIS: This is just a simple one of making sure that agendas are constructed and that panel discussion focusses on the quality of the evidence about reasonable and necessary rather than--in some ways--well; that's okay. I just think that is what didn't happen at the first panel that I was on, anyway.

DR. SOX: It sounds like structuring the agenda so there is plenty of time for discussion of the evidence is key. I think somebody else mentioned working with the Chair and CoChair of the panel to develop the questions that you are supposed to address rather than the HCFA staff sort of just doing it on their own.

Anybody else?

DR. FERGUSON: I just want to second that last point. I was going to say that in my remarks about our panel that we had a very crowded agenda and not enough discussion time. I think that that can be addressed.

DR. GARBER: I just want to clarify the sense of the Executive Committee since our panel is going to be meeting in early January before the Executive Committee will have another opportunity to meet. As I understand it, the motion that we approved means, in effect, that we endorse this concept that these

evaluations should focus first on what is the quality of the evidence and, second, what does the evidence say and that we could, therefore, organize our panel meetings accordingly.

Is that, indeed, the sense of what the motion meant, that we have passed?

DR. SOX: Yes.

DR. GARBER: The second issue that we could deal with between now and the next meeting or try to discuss today is this contentious issue of what does it mean to be effective. David Eddy had these two criteria. One is more effective than placebo. David, what is the other one? How do they compare to existing technologies.

I guess one of the questions is what if we have something that is clearly more effective than placebo and clearly inferior to commonly used treatments. Again, I am using the treatments incorrectly. I mean something much broader than that, other medical interventions, if you will, medical technologies.

How should the panels proceed? Does the Executive Committee want to provide any guidance at this point, discuss it at this point, or should that be deferred for a full consideration of the criteria and rules of evidence that we are going to develop?

DR. BROOK: I am concerned. The process, as I understand it, is any time two of us get together, it has to be done in a public meeting here at HCFA. We can't talk on the phone about any of this.

DR. SOX: Sharon, do you want to respond to that correct assertion?

MS. LAPPALAINEN: The committee can convene on operational issues but they cannot give advice and recommendation in closed session. It has to be open to the public. So, if you have an operational question, an informational question, you need a piece of data, call us up. You can call each other up. If you are on a fact-finding mission, these are operational things and that is fine, not subject to FACA. That is the Federal Advisory Committee Act.

DR. BROOK: Now let me come back. We can't do anything except in public around a table. Let me just find out if four of us met around a table for a day in an open room like this and didn't take any public comment, can we do that?

DR. SOX: Over a process issue?

DR. BROOK: Let's say we wanted to lay out the answer to this question. I believe we could do it in a day and get 90 percent there and give that as an advice document to HCFA. I am trying to figure out how we have to do it under this FACA process.

DR. SOX: Would it have to be a public meeting?

DR. BROOK: It would have to be a public meeting--

DR. SOX: No; that is a question, if it is a process issue rather than a discussion issue.

DR. BROOK: No; I believe it has to be a public meeting. At least my reading of this is that it has to be a public meeting.

DR. SOX: It might be more fun if it was.

DR. GARBER: Actually, Bob, maybe we could put this to Sharon in a slightly different way. If we agree on principle here about what, in broad terms, the evidence criteria would be, that clearly is a policy question that needs to be done in a public manner.

However, does it become operational when, say, groups of us meeting to draft specific language that is trying to put some flesh on the broad principle that was discussed here at the committee meeting. Is that an operational activity or is that something that has to be public--that is, just to draft a document--because I have to say, I haven't had much experience, or I should say any successful experience, drafting a document in a public meeting.

MS. LAPPALAINEN: I will tell you something. I feel a little uncomfortable answering this question because I am not counsel. I am not a lawyer and I do not have my general counsel here present to discuss this. But, generally, it becomes necessary to apply FACA if the government meets with--two people is considered a meeting, number one.

And, if you make any advice and recommendation outside of the public, then that is a violation because advice and recommendation has to be in the public. Meetings are only closed under certain circumstances that are defined in the FACA law, one of them being confidentiality, another one being if it is a judicial proceeding, another one if it is national security.

None of those apply to the Health Care Financing Administration.

DR. GARBER: Sharon, maybe I could rephrase it slightly. Suppose we take Bob's query and turn it into three or four people need to draft a document which is then presented to the Executive Committee in a public fashion and then discussed publicly. Is that in compliance with FACA?

DR. BROOK: How did the FDA develop their rules?

DR. GARBER: They only use government employees.

DR. BROOK: Can we do anything more than say we have the structure, we have heard what HCFA

wants to do. Our technical advice to HCFA is the things that we have talked about. One, they should come back to us with a document that basically allows the co-chairs and the chairs to participate in the questionmaking, in the drafting of the questions.

Can they even do that together without doing that in a public format? They ought to not just provide evidence tables but they ought to do some analysis and modeling, and they ought to try and do that. They ought to get the documents from the FDA and get the documents from the Preventative Services Task Force, which they probably have, and come back to us with a detailed structure that covers all these dimensions.

We could say that in a more detailed motion that we pass. But what I am asking is, given FACA, is there anything else we can do because of the limitations of how we can get together to give advice to the government.

DR. HILL: Mr. Chairman, I don't pretend to FACA expertise. I do know clearly that we couldn't reach a conclusion without an open and notified process. But the Deputy Director of the Coverage and Analysis Group is here, Dick Coyne, who had a lot of experience with designing the system and working it through the process.

So, if you would recognize him.

DR. SOX: Yes. Just so we are clear, I think we are talking about a process in which some people work off line, perhaps, let's say, meeting together for the sake of argument, to bring forward something that will, then, be discussed in an open forum with an opportunity for public comment before we take a vote. That is the process we are talking about.

MR. COYNE: Thank you. I appreciate the opportunity to be heard for a moment. Sharon, I would you to also comment on this, please, given your wealth of experience. My understanding of FACA is that the Executive Committee can empower a subcommittee to accomplish a task on its behalf. I believe you are headed right down that path provided, as you have postulated, that the result of the subcommittee's work is brought back to the committee, is discussed, has an opportunity for the public to understand it.

I know this is a bit cumbersome, but I think it is, perhaps, a way to accomplish what you are driving at and still meet the legal test. I can't give a definitive answer on that because, just like--there is never a lawyer around when you need one, at least not ours. God forbid, there is no shortage in the room.

So I do appreciate that. Thank you for listening to the comment.

DR. SOX: Thank you very much.

DR. BROOK: Can I ask a question about your comment? When you say we can empower a subcommittee, if we want to do any work on this--I want to get a specific answer to this question; either

we don't know and we will find out. If we wanted to help you do this--we were told before that we can't even send e-mail back and forth to each other on an operation.

We can't discuss almost anything because of FACA. So the problem is if we wanted to e-mail back and forth our comments about what the structure ought to be--somebody has said, "Look; I am a special government employee. I am going to work four days on this with government money to do this thing and I am going to task it out to a subcommittee. They are going to, then, comment on it and we are going to get it all back together so we can have something organized to present back here."

My understanding is that that is illegal. That is what I need a ruling on.

DR. SOX: Dick, do you want to respond?

DR. BROOK: Can we do that?

MS. LAPPALAINEN: If I could take a stab at it.

DR. SOX: Please.

MS. LAPPALAINEN: For the members in the audience, I am a recovering FDA employee. I worked at the Food and Drug Administration for nine years. I understand about that FD&C Act. I was most familiar with the Medical Device Amendments of '76 and its subsequent changes.

What the center for Devices and Radiological Health used to do was develop guidance documents based on things that they had heard at panel meetings. They would work on those guidance documents and they would, then, take them in a public manner to the panel.

However, the guidance documents were not regulation. These were a set of guidances which we would suggest people follow but they are under no regulatory authority to do so. We could do that with the panel.

DR. BROOK: Off line.

MS. LAPPALAINEN: On line, open committee.

DR. BROOK: I come back. I still don't know what we can do.

DR. SOX: Is it possible that we can't resolve this without your asking--you know what the question is. You have to consult with counsel and then advise us. I think we have probably taken this as far as we can go without getting the advice of counsel.

DR. HILL: I think we know what you want to do. What we will do is work with counsel to try to find out how we can make that happen consistent with the law.

DR. BROOK: I have another question for you. If we can't do that, since you have, on this Executive Committee, the six people that probably should be involved in that process, or at least six of the people that should probably be involved in that process, that have the most experience in that process, does that exclude them from having another relationship with somebody, from getting involved in this process? Because, now, I am really confused. If we can't do this through the panel because we can't do it, can Hal, through Dartmouth, contract with HCFA to help HCFA do this?

I am sorry for raising all these issues, but the process is what--

DR. SOX: I understand. I am sorry that we don't have the answer readily at hand to give you the parameters you need. Clearly, we should have that and we will next time.

Dick has got one more answer, if I can allow him.

MR. COYNE: Using our recent negotiated rulemaking on clinical labs as a precedent, Jackie Sheridan just pointed out to me, that was a FACA-compliant activity. Much of the work of that activity was accomplished via small work groups when, then, reported back to the overall body. No problems were raised about that activity.

So I go back to--if I were asked, my suggestion would be that, at minimum, I believe, the Executive Committee can employer a subcommittee to consider this issue, report back, and my supposition is that those committee members can speak among themselves on that matter.

DR. HILL: Privately; yes. I am going to suggest that we go ahead under the assumption that that is all right. Meanwhile, we will be working to check that with counsel. But I have to caution that you cannot, as a committee of the whole, devolve the ultimate decision to that subcommittee. You can't just send it to the subcommittee and bless it as if it was automatic.

You really do have to openly consider not accepting that recommendation or modifying it.

DR. BROOK: May I ask another thing for you to find out?

DR. SOX: Yes, sir.

DR. BROOK: If we are going to do that, does HCFA have both the ability and the desire to assign some staff to this subcommittee that can actually write up this document, recirculate, then act as the--does it have enough time and people to do that that can actually put all these materials together and do this?

If we said we wanted to do this in the next two months, does it have the budget and the ability to do that?

DR. HILL: We have the desire. As to whether we have the budget and the staff members, I would have to have a better sense of how big a thing you are talking about.

DR. BROOK: So that comes back to the last question. With those two uncertainties, should we not do anything in this regard at this moment? Is it prudent for us just to say that we would be happy to help out in this process consistent with the legal issues of FACA and what HCFA wants and offer technical advice and let it drop at that, regarding this? Do we need to do anything else for you that would help you move this process forward?

DR. HILL: I don't mean this facetiously; you have done enough. I have some clear understanding of what you want. I don't have a perfect understanding. I think I know what you want to do.

You can vote on something. If it is not cleared by FACA counsel, we won't be able to do it. If FACA counsel will clear it, we can go ahead with what we understand you to want.

DR. DAVIS: A couple of points. First of all, if what we need to do under the law requires us to delegate work to a subcommittee, it would probably be good to formalize that, I would think, in the form of a motion. So I would be happy to get that ball rolling.

So I would move that the Executive Committee authorize the Chair to appoint a subcommittee to work on this matter of evaluating a process for evaluating the evidence and to bring that back to the Executive Committee for its consideration at its earliest convenience and that we work with HCFA staff to determine how that could be done most efficiently and consistent with the interpretation of HCFA counsel, legal counsel, of what is permissible under the law.

DR. SOX: Is there a second to that motion?

DR. GARBER: I second.

DR. SOX: Any further discussion to that motion? All in favor, please raise your hands.

[Show of hands.]

DR. SOX: Any opposed?

[No response.].

DR. SOX: The motion carries.

Thank you very much. Was there something else you wanted to say?

DR. HILL: No; that will take care of it.

DR. SOX: You have done enough, as you said.

Any other last thoughts about what we can do for our panels before we get to the completed document?

DR. HILL: One other thought, Hal, if, just for the sake of argument, the legal counsel for HCFA determines that even the subcommittee has to operate under FACA, I don't think that precludes the subcommittee from doing work. The way I would envision it, you could get a quick announcement in the Federal Register that the subcommittee is going to meet in a week and let whoever wants to come from the public come, give them half an hour at the beginning and half an hour at the end or whatever the law requires, and let them give public comment.

But, in between those short periods of public comment, they have to let the subcommittee do its work uninterrupted. In other words, if we don't get the answer from legal counsel that we want, that doesn't mean nothing happens. It means you just have to operate under some limitation.

DR. SOX: More constraints. We will get there.

DR. BROOK: There is a third motion I wanted to deal with. We had asked HCFA to give us advice, and I don't know whether it is a motion, about whether--we have used the word "value." We stay away from the word "cost," but it is hard for me to understand value without cost.

I wonder if we can get a determination from HCFA whether we can include in the process, at the panel level, information about cost.

DR. SOX: Or cost-effectiveness.

DR. BROOK: Or cost-effectiveness or relative to the question that David raised about whether something cheaper that is infinitesimally much, much cheaper but infinitesimally worse than what is already out there is available, that that would not meet the standards of being assessed. So can we discuss that issue or even talk about the issue because that has been challenged as well.

DR. SOX: I think, unless anybody objects to pursuing that, we will just ask HCFA to pursue that and give us an answer.

DR. GARBER: Could I just ask a specific variant to that for HCFA to come back to us with, and the variant is can the panels, at their discretion, perhaps, or at the direction of this Executive Committee, consider cost or cost-effectiveness but, clearly, separate it in such a way that it is possible for HCFA to read our advice either with or without the cost information.

Let me be clear. I want this to provide an assessment that would meet everyone's goals exclusive of cost yet also provide information about cost for those parties who would find it relevant because I might add that, although we are empaneled in order to provide HCFA with advice regarding coverage, if this process is successful, many more people will be interested.

I don't think we should ignore the fact that people will look at us, if we are successful, as really an exemplary process in providing information that is broadly useful and broadly interesting.

DR. HILL: We will treat it as a subset question.

DR. SOX: If there are no other comments, then I think we need to move on to second part of the meeting with my thanks--

DR. EDDY: Do we need a vote on that?

DR. SOX: I don't think so. I don't think we do.

DR. BROOK: The question is, are we going to keep track of action items in our own structure and get a report back on these action items? How does that report come back? Does that come back at the meeting? I am just trying to deal with process here because--does that come back to the meeting or can people e-mail us that response back?

MS. LAPPALAINEN: Prior to every meeting, we discuss the old business and the standing issues that have been tabled at the previous meeting. We will also try to do that in a timely manner after the meeting. But it must be discussed also openly and that will occur at the next meeting.

DR. BROOK: If that is one question, can I ask one other question that HCFA can do?

DR. SOX: A quick one.

DR. BROOK: I believe in the developed world, there are a lot of different processes being used now to deal with coverage decisions in systems that vary from fee-for-service to competitive. If HCFA could put some of that together so that when we do our deliberations here at this meeting, we do them not in isolation from what other people, other processes that other countries are using to make these decisions.

DR. SOX: In other words, what are other people doing.

DR. BROOK: I would like a spreadsheet about how Switzerland, France, Germany, the U.K, Australia, New Zealand is handling these questions so that the work that we do is put within some comparative--we take advantage of people that have dealt with a lot of these issues for a long time, just like we have.

DR. EDDY: And HCFA staff can make site visits to all those different countries to collect that information.

DR. SOX: With that, we will move on to the second half of the meeting where we are going to discuss two actions of our panels.

I would like to start by hearing from you about exactly what our options are as a panel when we come to our active approval or disapproval, or whatever.

DR. HILL: Thank you, Mr. Chairman, let me review what we said this morning. The MCAC Executive Committee, as established in the charter to provide guidance to panels, facilitate substantive coordination among panels and review and ratify panel reports and submit the report to HCFA. I interpret that, and my understanding of that is, that you are called upon to review and ratify which implies that you may choose not to ratify.

It is an off-on switch. I don't know that there are any other options in the charter for you although we would sure like to hear your reasons for whatever action you take.

DR. SOX: Part of the reason for giving reasons is to try to develop the sort of case law that will help us as we move forward and develop a real history with this advisory committee.

So, with that, I would like to start by asking Dr. Ferguson, who is going to talk about human tumor-assay systems to tell us about what happened in his committee meeting. Specifically, I am interested in knowing how much time there was for discussion, his impression about that discussion, if it is possible, John, for you identify what were the key pieces of evidence that seemed to drive your panel's thinking. I think that would help us a great deal.

I think, then, it will be up to us to discuss that evidence and discuss that process and make a decision about whether to ratify or not.

Review of Medical Specialty Panel Recommendation

DR. FERGUSON: Thank you, Mr. Chairman. Also, after I am finished, Dr. Murray, our Co-Chair, will make a few remarks, too.

We were presented with many different tests from several different companies involving many cancers, many drugs. The number of combinations and permutations was tremendous. Many of these had a long track record. The investigators had been involved for many years. They had learned along the way and so on, and this technology had evolved, but it had evolved in a number of different directions.

This led to a couple of problems in my view. Number one, we, as a panel, felt that we sort of had to

handle it in an umbrella fashion. Actually, the questions, as they were presented to us from HCFA were in that form; that is, looking at all these tests sort of as one kind of test.

This led to a second problem in which the agenda was, as has been mentioned, too packed. There were a large number of presentations and the times were unequal. There was virtually no discussion time between any of these talks, some at the end. But I felt that we had to cut back some presentations that might have gone more.

So this was, in my view, a problem. Because of the variety of technologies and the number of speakers, we were compressed in time with little discussion time and had to handle it in an umbrella fashion, which I think was not satisfactory for all.

I must say that I think that the protagonists of these were under the gun also and not just HCFA or our panel. I think that it is possible to have fifteen- or twenty-minute presentations, that the timing could be done by HCFA, setting the agenda that way and have more discussion time. I think that is quite possible, to present the high points when there are number of speakers.

Another issue, in my view, was that HCFA had had a number of people critiquing what was presented. Some of the critiques actually involved one single paper by Kern and Weisenthal. I am not sure that that was the best way to handle that; that is, two speakers from AHCPR, Dr. Handelsman and Dr. Burke, both critiqued that one paper.

I think that that was an extremely small and narrow view of the whole business. Another was that the NCI representative presented a paper which, in my view, I was a bit disappointed in coming from my old former institution that it did not seem to me to be up to date and lacked in that aspect.

So I am not certain that the protagonists were given all the critique information. We didn't have it. I didn't have Dr. Burke's entire presentation in my folder. We tried to give the protagonists time to respond. I think that that could be done a little bit better in the sense that if all the critiques of presented papers could be given to the presenters in advance, they might have time to prepare some rebuttal and response to the critiques.

I think that the questions prepared by HCFA, as I mentioned before, I think I can understand how the questions are arrived at to some extent, but since HCFA would like the panels to really hone down and answer whether or not they should be paying for these things, although I think they are not asking us these questions.

I must say that one of the questions I was presented with was actually stated about should HCFA cover this if the test shows that it is not responsive to this drug. We changed the question.

So I think that the questions are a big problem and I don't have a ready answer. I always have thought that questions that could be answered yes or no are not the best for these kinds of forums. They were not

in the consensus program. But it may be that when one is presenting a motion to a panel to vote yes or no, then yes or no answers are, perhaps, the best, although I am not sure they get at everything.

The evidence, I think, and I would kind of like to bounce this off of Dr. Sox because he has written about it, and that is that the number of randomized controlled clinical trials with outcomes measures for diagnostic tests is, as far as I know, extremely small and minimal. These human tumor assay systems, in my view at least, fall in the realm of diagnostic tests.

One of our temporary panel members, Dr. Loy, pointed out that they were not diagnostic tests but I think one could view them as such because even if they might be a more specific kind, responding to certain molecular, biological and genetic things in these tumors, why they are sensitive or not.

So I think, in that sense, that they are diagnostic tests. To request randomized trials for these kinds of things, I think is proper. On the other hand, historically, I can't think of anything that I use in neurology practically in a diagnostics has been evaluated with the randomized trial, at least extremely few.

Hal, do you want to say a little bit about just diagnostic tests and randomized trials?

DR. SOX: I don't think there are many studies outside of the screening literature where people have been randomized and then used an outcome like death from the disease you screening for as the principle endpoint for the study. Certainly, one question to ask is would it be reasonable to do a randomized trial. There might be some situations where that would be more reasonable than others.

I could see that this might be one of those situations where you have patients who have metastatic cancer where you have a test that directly drives the treatment that is going to determine their length of life. But on the broad answer to your question about are randomized trials the rule for diagnostic tests, the answer is certainly no.

DR. FERGUSON: I think that this was a point. My sense was, from looking at the literature and what I heard, was that some of the trials, the studies, regarding chronic lymphocytic leukemia did have survival measures and comparison groups and a number of other trials had comparison groups, sometimes concurrent and sometimes historical comparison groups.

I thought, just personally, that the literature for CLL was certainly coming up to snuff and was very reasonable. So the others were suggestive and not as good, not as persuasive. Our panel was, I think, persuaded that these tests were more effective than, perhaps, even I thought and I didn't have to vote. There were no ties that I had to break.

Bob, do you want to--

DR. MURRAY: I will keep my comments very short because, basically, I second everything that Dr. Ferguson just explained. At first glance, this seemed like a rather straightforward issue. There seems to

be a parallel with the very commonly performed urine culture or blood culture for the effectiveness of different antibiotics. So, initially, it appeared that there was a parallel and it should be evaluated as an in vitro diagnostic procedure.

On closer examination, it was not a simple two-by-two matrix but a two-by-three-by-four-by-two-by-three. So we were evaluating many different facets. The different assays that we examined had different methodologies. Some examined cell growth. Some examined cell death.

They had different strategies for testing; that is, some used physiologically achievable chemotherapeutic concentrations whereas others used supra-physiological, high-dose, in vitro assays. Some of them looked for exclusion of ineffective chemotherapeutic agents while others attempted to identify effective chemotherapeutic agents.

As Dr. Ferguson mentioned, they used different evaluation criteria. So it was a much more complex evaluation than we initially thought. Was there enough time for listening to comments for studying the data? I think not. In retrospect, this type of an analysis would have been much more effective if it had been conducted over two meetings separated by several months or at least by a period of time.

I know that that is very difficult to achieve, given the resources that are necessary to put together even a single meeting. Yet, when presented with a very significant amount of data plus the presentations, it is difficult to digest all of the information and then to stand back and perform a reasonable, logical evaluation.

In addition, I should comment that, in addition to evaluating the cold, hard scientific facts, it was also necessary to evaluate the potential for conflict of interest since the proponents of these tests, in many cases, had interests in the commercial offering of the services.

I think it might have been helpful if the packets of material, the binders, that were provided were organized slightly differently. We have already heard earlier this morning that evaluation of the papers, of the scientific articles, it would be helpful if these were categorized in advance and I certainly concur in that recommendation.

Secondly, in the material that was presented, it was generally organized, not exclusively but generally, by the proponents. So there were mixtures of background information, chapters from textbooks, for example, basic review articles which gave good overviews and then recent research modifications of strategies.

At least on first glance--it is in Section 3 of this book, of the binder that we received--it is difficult to put all of that in perspective in the space of one day-and-a-half meeting.

Lastly, the questions, as Dr. Ferguson mentioned, needed modification. I think that the panel as a whole did its best to step back from the data, identified that yes, there is sound scientific evidence, but the

evidence is not as clear-cut, would not warrant a yes or no answer to the questions as drafted, and that is why you will see, in the minutes of the meeting, that the motions that were voted upon are, in almost all cases, reworded questions.

I think that is all that I have.

DR. SOX: Thank you. We are a little bit in an improvisatory mode here as a committee trying to evaluate this recommendation. Perhaps, at future meetings, we will decide to have somebody who was not a chair or co-chair of the panel make an independent review of the data that was presented in order to help advise us. But we will just have to do with what we have in the way of volunteer efforts along those lines.

I thought I might start out by asking Dr. Eddy and Dr. Garber, who have done a lot of work on the evaluation of diagnostic tests which presents, in many ways, a much more complicated problem of evaluation than a treatment to make any comments they wish about this body of evidence and how they would help us to think about it logically.

Which one of you would like to start?

DR. EDDY: First I have to admit that I have not studied this body of literature or evidence in detail, so I don't want you to take anything I say to be based on that. So my comments will be more general.

As John indicated, the evaluation of diagnostic tests is fundamentally different and more difficult than the evaluation of treatments. With the evaluation of treatments, you can often, and should always try to, get your hands on direct evidence that relates the treatment to the health outcome.

In the case of diagnostic tests, as has been said, that is very rarely true. So the only way to evaluate it is to use indirect evidence or some sort of a modeling approach. There are very good modeling approaches. They ask several questions in sequence. First, if you perform the test, can you find the conditions you are looking at. We have measures of how well the tests do find those things, the true positive rate or the sensitivity.

We are also interested in the extent to which the test will find conditions other than the ones you are interested in but which might require workup and cause patient and morbidity and so forth. We encode that in the false-positive rate and so forth.

So the first set of questions has to do with whether or not the test can find the condition. Then the second set of questions has to do with whether or not the information provided by the test, the finding of the condition of positive test result, actually causes people to change their behavior.

In this case, it would be whether or not the performance of these tests would cause people to choose different chemotherapeutic approaches to a patient. You can look for evidence for that.

If you don't have direct evidence of that, an indirect measure of that might be something like the predictive values which would tell you whether or not people should change their treatment strategies based on a positive or a negative result.

The third set of questions comes up which is, if you do change your treatment of the basis of a test result, does that, in fact, change health outcomes. That question can also be examined through the evidence. So it is possible to break to problem down into--I had it into three parts; with some problems it is more complicated than that--look for evidence for each part and then kind of reconstruct them, try to get a qualitative or, in many cases, a quantitative understanding of how the performance of the test would change health outcomes.

Now, that is extremely difficult to do if you have one test, one condition, one set of patient indications, a dichotomous outcome, it is either positive or negative, and so forth. As I have heard this, you had multiple tests of different types, different mechanisms of action, different patient conditions, different treatments and so forth.

So I can appreciate what I have heard about this problem being fiendishly complex. I can appreciate that, from what it sounds like to me, it probably was too difficult, too complex, for a panel to do in the amount of time that it had.

When you add, on top of that, the fact that we want to give substantial amount of time to people to present to the public and to proponents to present information, then the time becomes even more squeezed.

A sort of impression that I formed listening to the presentations thus far and, also, reading some of the cover material, some of the letters that were presented, is that I can certainly appreciate if this panel felt that it did not have sufficient time to really arrive at a carefully judged conclusion.

DR. SOX: Alan, do you wish to comment?

DR. GARBER: I think David really explained the general situation with diagnostic tests. I just want to add a couple of other things that I think are pertinent in a situation like this. One of them that came up with regard to these particular tests is that the measure of the superiority of one test as compared to another is really captured in the receiver operating characteristics curve.

One of the difficulties in pulling studies of a diagnostic technology is usually they don't tell you what is the receiver operating characteristics curve is. The receiver operator characteristics curve is a measure of the sensitivity and specificity. Basically, if you change the threshold for what you call an abnormal test, you change both numbers at the same time. The receiving operator characteristics curves map out that entire relationship.

The problem is you can't tell from the different studies or different tests that you are comparing or different studies of the same test whether they are talking about two different points on the same ROC curve which would be an indication that the tests are very similar in performance or if they are talking about two different ROC curves.

Basically, the problem is you are trying to infer something about an entire curve from one point which is impossible. So one of the big issues that you face here is how can you meaningfully combine the results of different studies.

This is on top of a more generic problem which is true of treatment studies as well as diagnostic studies; that is, how similar do things need to be--that is, different treatments or different tests--for you to say, "We can analyze them altogether, lump them together. That was obviously a big problem here.

Or can you lump together the use in one disease with the use in another disease. Is this a chemotherapy-specific question or is this a disease-specific question and so on and so forth. But the bottom line is--I agree with what David said. Even as diagnostic technologies go, this particular one entailed an unusual degree of complexity. An unusual number of judgement calls had to be made in order to draw any conclusions.

DR. SOX: I have looked at this test some and tried to at least begin the sort of analysis that Dave and Alan were calling for. It is extremely difficult to do that because the table, for example, in Dr. DeVita's article which summarizes some eight or nine articles that try to measure the performance of this test in predicting a patient's response to chemotherapy, we don't know what the specific disease was for which they were treated.

And we don't know whether the test represented a whole bunch of different patients with different diseases or a bunch of patients with a single disease.

But, overall, if you just look at the bottom line of this particular table, the test seems to increase the odds if it is positive--that is, showing sensitivity of the tumor to the agent. It increases the odds the patient will respond to the agent by a factor of four.

When it shows that the patient is resistant, then the chance of the patient responding to the agent anyway drops to about 20 percent of the starting odds. So it moves the probabilities of the odds sort of moderately well, as diagnostic tests go.

You would like to have a test that increases the odds by a factor of 100 and drops the odds to 1 percent of the starting odds. That would be a wonderful test. This is sort of an average test.

If you take the overall prevalence of people being sensitive to the chemotherapy as the overall prevalence in this particular group of studies, about 40 percent of patients are sensitive to the chemotherapeutic agent that is being tested. Given that information, you calculate that the probability of

a person being sensitive to the agent, given that the test shows that they are sensitive, is about 71 percent.

So it increases it at a fairly high chance that they are going to be sensitive if the test shows they are sensitive. If it shows they are not sensitive, it drops the probability of their being sensitive down to about 10Êpercent. So that is a crude analysis of a crude dataset, but at least it gives us some idea about how much this test changes probabilities and to what level.

DR. BROOK: I don't know why HCFA sent this one to us, but I view it as the beginning of what is going to be this whole process of genome-tailored drugs and diagnostic tests. That is why I am taking this very seriously. Regardless of what we do with this panel, we need to begin the process of answering all the questions that were raised around this table, of what is going to be the scientific method for addressing this question.

The downside of a test that identifies whether somebody is going to respond to something with moderate odds is that that something might be more dangerous than something that the doctor might have used otherwise. So they could have responded but it could have killed them at much higher rates as well and the tradeoff that is responding versus outcome is not in a favorable direction.

I am not saying that is what this literature shows. What I am saying is we don't have the foggiest idea--at least, I haven't seen--what the principles are going to be for putting together the evidence. It is going to happen in hypertension. It is going to happen in diabetes. It is going to happen in every disease where people are going to come forward and say, "I have a diagnostic test which will indicate that you will get benefit from this drug and you won't be harmed by it because you are missing this enzyme or this piece of thing," and it is going to be a person-tailored approach.

That is where medicine, presumably, is going if you look at the big picture, that we all will go through a whole slew of diagnostic tests and, out of this range, we will get this drug because of our genome makeup.

So this is the first salvo of this, in this area, at least, at least in terms of coverage that we seen explicitly in the public process. So, is there some way that we could urge, give some technical advice to HCFA, that a serious dialogue, regardless of what we do here, begin to be undertaken about how we are going to tackle this problem before we are left with the genome being decoded and some more, 5,000, of these decisions coming to HCFA about what to do, so we can being to mythologically address this question, that this is an urgent question, to figure out how we are going to put the evidence together.

DR. SOX: I think it is an urgent question and it is one that, I think, a formal recommendation from this committee to HCFA would be in the public interest.

DR. BROOK: Does anyone know whether the NIH is doing any work on this on figuring out how, really, evidence would need to be put together to use this whole new branch of diagnostic testing? I don't think AHCPR is doing anything. Does anyone now if there is anything going on?

DR. SOX: I don't.

DR. BROOK: I am wondering whether we ought to, independent of our committee, recommend that HCFA at least advise the Secretary--I would advise the Secretary on that that this is a technical issue, or advise somebody, whoever we can advise--I know Sharon is raising her hand--whoever we can advise that this is something--that serious methodologic research is needed.

DR. SOX: Bob, this is an important issue that you have raised. I think I would like to ask you to craft a motion, perhaps, that, if we have time, we can come back to at this meeting, if not make a specific place in our agenda for next time.

DR. BROOK: May I ask another question on the comparative issue? The thing that comes closest to this is the allergy testing process, the different kinds of tests for allergy and then the different kinds of diagnostics and outcomes. There have been, as you know, lately, a few studies that are actually looked at, outcomes from different processes using these kinds of tests.

Is there some precedent about what was done in terms of coverage of those tests and what kind of evidence was used to make those decisions that could have been used to help guide this panel in that process?

MS. LAPPALAINEN: If I may, on your first question, who would look at these kinds of things, specifically, you mentioned genetic markers and molecular diagnostics. The Secretary of Health and Human Services has put together an advisory committee on this.

DR. BROOK: To look at how to develop evidence?

MS. LAPPALAINEN: To look at, specifically, genetics and molecular diagnostics. That advisory committee falls under the offices of at least three agencies that I can recall off the top of my head. They are NIH, the Food and Drug Administration and the Health Care Financing Administration.

So there has been a committee that will look at genetics and molecular diagnostic devices. However, the human tumor assay systems were not molecular or genetic.

DR. BROOK: So they are not included?

DR. FERGUSON: Right; they wouldn't be at this point. The Genome Project does have an ethical, legal, social issues portion of it, both at the NIH and at the DOE.

MS. LAPPALAINEN: Ethicists are required to sit on the committee.

DR. SOX: We need to get back on point because we really have to talk about whether or not we think

that this test ought to be covered by HCFA. What I would actually like to do is hear from everybody briefly about sort of what your take on it is.

Leslie, if you have another point, perhaps, you could raise that and then I am going to start with you.

DR. FRANCIS: I will just raise it as a question. I would like to hear more from the two folks from the panel about why the panel concluded that clinical response, rather than survival rates, should be the--actually, they concluded that both--and I want to know what their discussion was about why clinical response should be accepted as an appropriate measure of clinical utility.

It would help me in evaluating what you said to hear your comments on that.

DR. FERGUSON: We had very little survival information. There was some on the CO ones. I don't remember of there were other ones.

DR. SOX: The Chinese study had survival.

DR. FERGUSON: The Chinese one did have survival; yes. I am not sure I can give you the entire reasoning except that we felt that, at least in the diagnostic-type test, that tumor response was reasonable. I would be applying a far higher standard to ask for survival on all diagnostic tests. Maybe there are other comments.

DR. MURRAY: I wish I could give a very clear-cut answer, but we did have one oncologist on the committee who was there as a temporary voting member. She accepted this as an adequate measure so I think that, since these were generally papers written by oncologists, we followed her lead.

DR. FRANCIS: Did it correlate, in any way, with any improvement either in quality of life or length of life for the patient? That is my question, really.

DR. SOX: There was the Chinese study which, I think, was done on patients with metastatic breast cancer. The response rate, again, whether it was complete or partial--I don't remember--was 43 percent in the group that didn't get tested and 76 percent in those that did, quite a large difference.

The actual duration of the response was essentially the same, about six or eight months in both groups, and the median survival was 18, I think, in the group that got tested and 17 in the group that didn't get tested. Small study. Small differences. So that is one example where a big difference in response rate didn't seem to translate into better survival or even duration of response.

DR. EDDY: Just one more quick example. In high-dose chemotherapy for metastatic breast cancer, high-dose chemotherapy delivers wonderful complete and partial responses. But when we finally got around to doing randomized, controlled trials, we just didn't see it in the survival rates.

But, to be fair, we have to understand here--let's see. We are not talking about whether response rate is an appropriate measure for the effectiveness of a treatment. I think it was just chosen for this particular example because that is as far as they could go with the literature they had pertaining to the test.

To have gone beyond that, they would have had to have developed a sort of sequential analysis involving modeling and so forth. That can be done, but it takes a very extensive workup, very well organized information and some modeling in order to do it.

I can appreciate that they simply didn't have time to do that in this particular exercise.

DR. SOX: One more comment that I just want to briefly hear from everybody about what their take is and then we will go on.

DR. BROOK: Since they couldn't resolve this evidence in two days, I don't think we can resolve this evidence without hearing anybody in one hour. I am wondering what the comments ought to be for the panel. It is not about the evidence but what we heard about the process of the meeting. At least, I heard nobody say they were happy with the process, of our sort of people, said they were happy with the process and had enough either synthesis, analysis, time or whatever to come up with a reasoned conclusion.

They almost--both the chair and the co-chair, basically, said to us, didn't they, that they didn't have a lot of confidence in anything that came out of this panel because of the process.

Should we respect that by saying, then, let's give them more time to answer the question correctly?

DR. SOX: That is, actually, what I would like to have--

DR. FERGUSON: I am not so sure I could say that. I think that we had quite a number of people on our panel whose opinions and views I would respect and I do respect. I thought our panel's discussion on the second day covered a lot of the problems that we saw. I can't, personally, say that we did a bad job with what time we had and the huge amount of variety in what we were asked to look at.

So I, personally, wasn't terribly impressed with great evidence. On the other hand, and as long as I have been involved in this business with the Technology Assessment Committee here and at the American Academy of Neurology and at the Consensus Program at the NIH, I have seen worse.

DR. MAVES: My comment was kind of concentrated on the process as well. I realize that we are bound to a public, open process but it may well be--and I appreciate the comments of the Chair. I was not there and so these should not be construed as specific criticism in any way, but maybe it is too much to expect to come to the conclusion in a day and a half or in a process when you are both evaluating data, discussing data, looking at studies, getting public comment back.

I wonder if, in fact, consideration, as we begin looking at our process, of a two-step process, of having a moment to sort of go back, think about it quietly, yourself, independently, if you will, gather again in a public forum. My only point in bringing this up was that it seems, in many ways, that this is an awful lot to ask of a process where you are both trying to satisfy kind of a scientific agenda of going through the materials, a political agenda of, obviously, allowing the public and other individuals to have free access to the system, and then come up with a conclusion at the end of that time, in some sense of time and scientific/politic pressure, may be one of the things that we would want to look at as we look at our process.

DR. SOX: I guess you are raising, to some degree, your level of confidence in whether this stuff works or not.

DR. MAVES: Yes.

DR. SOX: Anybody else want to comment before we move on?

DR. DAVIS: I have a couple of comments about process. First of all, because we are forming a subcommittee to help us figure out how to approach the evidence, I think we also need to talk about to what extent do we need a protocol for doing that that is specific to each panel. The subcommittee may come up with something that serves us well overall or may serve two or three of the six panels well, but there are going to be special considerations for diagnostics and for medical devices and for prosthetics and all these other things.

We have already talked about our CTs sometimes are rarely done, are not applicable to some of the things that we are going to be considering. So my first comment is that I think the subcommittee needs to look at a protocol but to what extent do we need to develop a different protocol or a more specific protocol for certain panels, we may need to bring in some people from those specific panels when we get down to that second layer.

Once we get to that point, and you start going through a good process, how do things get fed back up to the Executive Committee. If we are to respond to what we have gotten from the first two panels, if I understand correctly--I have tried to go through this materials but I might have missed something--we have the questions that were posed to them answered in the minutes and then a lot of background material.

Was there a formal report that we were given from each panel? I would envision, down the road, that the best way to handle the process would be that the panel would put together a report and that report would look at each question. And then, for each question, it would say, using the protocol that we have decided on, here is what the evidence is and here is the quality of the evidence and here are the conclusions. And that would come up to the Executive Committee.

DR. SOX: Do you want to respond specifically to that?

MS. LAPPALAINEN: Regarding the panel report, the summary minutes that you have are a FACA requirement. This is required by law. The other half of that report are the transcripts that are also required by law. So what you have, the combination of that, is the report and that should adequately summarize what occurred and what conclusions were made at that panel meeting.

Were any additional analyses to be done by the panel to be made into a report, it would have to be done in an open public manner.

DR. BERGTHOLD: I think it is more a matter of proportion. If you look at these minutes, there are twelve pages. Only one page is devoted to the panel recommendations. So, if I may, I think that there is a way to maybe expand the discussion, itself, without getting into a transcript situation. Is there a middle ground is what I asking.

DR. SOX: I think we know what we want. We have got to figure out a way to get it within the framework that we are operating in.

DR. GARBER: I think that one approach to get at what Ron was driving at is to change the ordering a little bit of what he proposed and that is to say staff prepares the report before the meeting. That is what these evidence tables, or whatever it is that we are going to recommend, amounts to, a structured way to look at the data that are out there.

And then the panel would spend more of its time discussing aspects of that report rather than starting out with essentially undigested studies and testimony and so on in trying to assemble something because I agree that two days usually won't be enough time to do that whereas four hours of panel time may be enough, may be more than enough. In fact, if there is a good evidence report well assembled beforehand, it doesn't mean that the panel accepts everything that is in there, but their discussion is organized around the report and they can point out areas of agreement and areas of disagreement.

I think it makes for a much more efficient process to accomplish the same goals. I don't think this raises any FACA issues. We are talking about a staff report, or one thing that we had discussed is maybe evidence-based practice centers preparing the reports in advance.

So we take a different approach. You start with something that is much more precisely organized. In this particular context, I think, in fact, one of the difficulties and, since I wasn't at the meeting, I really don't know for sure--I am just speculating--is that it may not have highlighted the real critical issues the way a preassembled report would have.

It sounds to me that at least one aspect, in this particular case, has to do with surrogate endpoints which is, really, a generic issue, nothing unique to this diagnostic technology; that is, if the most extensive trial you have reports partial or complete response rates, is that enough for us to conclude that the testing improves the health outcome.

Or do you say that you need to have more direct evidence of survival benefit. I think this is what Leslie was getting at with her questions. That focuses your discussion because my guess is that sometimes the panel would say that is sufficient and sometimes they will decide it is not. It is based on all kinds of other evidence that link the surrogate endpoint, i.e., the complete response rate, to the ultimate health outcome that we are concerned about which might be survival or disease-free survival or something like that.

You can become much more efficient if you go into the meeting with the critical areas for discussion outlined in advance. I am very impressed with, also, the literature that was provided, that some of it was right on target. But a large fraction of it was largely irrelevant to the key issues that are being discussed.

DR. SOX: These are a lot of process questions that I hope we are going to be able to address that have to do with agenda setting and so forth.

I have decided that we are not going to take a formal break but move straight on through because we are going to run out of time fairly quickly. Sharon wanted to make a couple of comments and then we will move directly into the second panel's presentation.

MS. LAPPALAINEN: Over the lunch break, we did get a ruling from our general counsel regarding subcommittee work off-line. Our counsel advised us that if a subcommittee and its charge is clearly articulated in the record--for example, the motion that has been passed here today, the subcommittee can work off-line and develop a product.

In order to be formally recognized, discussion of the product and any decision about it must occur in a properly announced open meeting. So subcommittee actions are discussed in the FACA regulations as being all right.

DR. BROOK: Do you want a motion about this, Hal?

DR. SOX: About what?

DR. BROOK: About this report? Do we have to do anything about this other than talk about process?

DR. SOX: If you mean are we going to take a vote on whether to ratify or not; is that what you are asking?

DR. BROOK: Yes.

DR. SOX: That actually will happen right at the end of the meeting after the public comments.

DR. BROOK: We are going to do the other one first and then come back?

DR. SOX: Yes.

DR. BROOK: Because they are very different.

DR. SOX: Sharon is leaving so that she can arrange our cabs for those of us who are anxious about making our flight schedules.

We will now turn to Dr. Holohan to discuss the myeloma treatment discussion.

Review of the Medical Specialty Panel

Recommendation

DR. HOLOHAN: Thank you. I think I can save some of our time by making a fairly global statement that some of the process issues already discussed for the Tumor Cell Assay Panel were also operative with our panel.

You probably have seen in the handouts that I took the option, which I was told that I was permitted to do, of writing a dissenting opinion as a non-voting chair from the conclusions of the panel. While I have great personal and professional regard for the panel, I thought that the conclusions were ill-advised in that they were not based upon the evidence that was provided either prior to the meeting in writing or by the evidence presented by the proponents of this treatment.

Let me first go through some structure problems that I saw, and I am going to ask two of the panel members who are also present here today to comment about this at the end of my presentation.

The material provided was simply provided in the format of photocopied published studies. I think Dr. Francis has made the comment earlier that she found that, as she presumed some of the non-physician members did, not a particularly useful way of providing information to her to digest prior to the meeting.

If you look at the questions, the formal questions that our panel was posed, I would submit that the first question, "Is there sufficient evidence to support autologous stem-cell transplantation for the treatment of myeloma," et cetera, is a fairly vague question. What is meant by "to support autologous stem-cell transplantation?"

It does not ask if it is safe and effective compared to the alternative treatments. It does not ask whether it is equal to standard care. It does not ask about risks or benefits. It is conceivable that some panel members voted the way they did because they thought there was evidence to show that this might, or possibly, have some benefit.

The second question is even more vague; "What factors should be considered when developing coverage

policy for autologous stem-cell transplantation?" Again, no specificity as to what is meant by, "what factors."

Question No. 5; "What qualifications should apply for providers and centers performing the autologous stem-cell transplantation procedure?" You will see that the panel concluded that a center should be certified by some body which, again, was left vague and unspecified.

So I thought that the panel probably was a little behind the power curve initially in terms of the questions that they believed they had to respond to. In addition, verbal instructions were given that I thought limited what the panel could do.

For example, we were specifically told that it was not considered appropriate to recommend to HCFA that coverage be provided only in the context of a prospective trial which I thought removed an option that could have been very significant for the panel.

There was a time problem. I appreciate the interest in and, indeed, the legal need for public input and comment. There was far too little time available for the panel to actually discuss the evidence and ask some of the harder questions.

At some point during the presentation, I felt like a second-year medical student again watching interminable slides telling me all about the epidemiologic of multiple myeloma which I really didn't need to know and which none of the panel members needed to know in order to evaluate the evidence and come to their own conclusions.

To some extent, this was not under HCFA's control because there was a hurricane which occurred at about that point in time and all of the people from out of town were concerned about being able to evacuate the Baltimore area and return to distant homes, most of whom were unable to do that. That was not under the control of any federal authority, believe it or not, but it certainly impacted on the availability of time for further discussion which I think would have been useful to the panel members.

Finally, there were a number of inconsistencies in the information and the testimony presented by proponents. I do not think and, perhaps, to some extent, this is my fault as chair although I tried to be even-handed, a lot of the inconsistencies were not called to the attention of the proponents. I will get to a few examples of that.

Having said that, you have a handout that I have just passed around. When I read this material prior to the panel meeting, perhaps I was prescient. I saw a problem in the panel being able to evaluate all of that material. I provided for all the panel members a fairly simplistic chart showing the levels of evidence taken from Sackett et al.

The major point that I was trying to make with this was that expert opinion, which I was sure we would get a lot of, and we did, in case series tend to fall at the bottom. What I also did was to try to stratify all

of the written material provided prior to the meeting in two sheets of paper.

One you will see is published reports provided from the Health Care Financing Administration. The second were reports or studies provided by proponents of high-dose chemotherapy and stem-cell support for myeloma. Since Dr. Sox asked me to do this, I will briefly take you through this which I hope will illustrate why I have serious reservations about the final conclusions of the panel.

In the materials provided by HCFA, the first is kind of the gold standard in this arena, the study by the French Intergroup published in the New England Journal of Medicine was a prospective randomized controlled trial. It is the only prospective randomized controlled trial ever completed or published in the treatment of multiple myeloma with this particular therapy.

I call your attention to the column that says "percent of patients greater than 65 year; none." None of the patients entered in the French trial were of the age that is ordinarily considered the standard age of entry as a Medicare beneficiary, excluding the end-stage renal-disease patients and those who were totally disabled.

In the Comments Section, you will notice that, even in this randomized trial, only three-quarters of the people who were assigned to the high-dose chemotherapy group received that. Only three-quarters of them received the full regimen.

So one-quarter, who end up, of course, in the survival figures never actually got that because the analyses were done on the basis of an intention-to-treat. If you look at patients who were over 60, between 60 and 65, the exclusion criteria, less than 60 percent of those between 60 and 65 completed or were able to tolerate the high-dose chemotherapy.

The next study, Fermand, is really just a study of early versus late high-dose treatment. All patients receive high-dose treatment. There was no difference. But, again, you see the exclusion criteria in that study are age greater than 56.

There is a study, actually provided by HCFA, that used the dreaded words "cost effectiveness." The only comment I would make about that is, again, if you look at the exclusion criteria, you see that where specified--NR means not-reported--there appears to be some significant difference in the viewpoints of the clinicians performing these studies as to whether diffusion capacities for pulmonary function should be used, what the maximum renal function disability should be, et cetera.

The authors of this paper assumed in their study that charges were equal to costs, which we all know is not true.

Siegel's study alleged to show that older patients could tolerate this well. There are some problems with intrinsic biases here. I will simply point out that the patients who were over 65 were 49 who were selected from a larger group of 900 patients, hardly a ringing endorsement for treating of elderly patients.

Those 65 were matched to 49 of 500 patients who were less than 65 for a few factors that are known to be prognostic factors. The difficulty with that, of course, is we don't know what all of the prognostic factors may be. I don't think, unless someone has a question, there is much point in going over the retrospective case series of book chapters and the practice guidelines except to note that the guidelines, themselves, some of which are actually in our handout today, defined them as a "consensus of authors reflecting their views." It doesn't refer to evidence.

In the reports provided by the proponents and supplied to the panel prior to the meeting, Siegel and Attal's paper were provided also by HCFA and are represented on the first matrix.

Four pieces of unpublished data were provided. Three of those four pieces were simply figures from some report not otherwise specified and an unpublished paper, a case series, by Palumbo. Again, if you look, the exclusion criteria in this case are fairly vague. They included, in the case series, everybody who didn't have an exclusion criteria and the exclusion criteria were basically abnormal organ function.

Attal also provided an abstract which appears in the material provided prior to this meeting which was an update of the original New England Journal study. As good a study as I think that is, you should note that the material published in the New England Journal gave an actuarial five-year survival comparison.

Attal updated that with a six-year actual--not statistical; actual--survival, both event-free survival and overall survival. Although the differences still favored the high-dose group, the overall survival decreased from the actuarial data by 20 percent in the high-dose group and increased by 75 percent in the standard therapy group.

The event-free survival diminished in the high-dose group from the original actuarial data by 14 percent by increased by 50 percent in the standard treatment patient group.

Dr. Barlogie provided another paper, a case series, comparing the outcomes in total therapy, his approach to this, and compared his 123 patients, only three-quarters of which actually completed the therapy, to 116 SWOG patients selected out of a larger group of 1123. I emphasized age because this is an issue, and the age was matched, according to the author, within a decade which is not an impressive match to me from my personal point of view.

Another study was done looking at retrospective cost effectiveness. To me, the operative sentence from this paper and the conclusion is that "these indirect comparisons cannot provide conclusive data."

Dr. Kyle, who was one of the proponents who testified, published a review in Seminars of Oncology which, really, is not evidence in the sense that we tend to think of it; it was a nonsystematic collection of previously published information. It is in here because Dr. Kyle stated, in that paper, that further prospective randomized controlled trials are needed.

When he was asked about that statement, subsequent to his testimony, in material he published and provided, he said, "Well, I meant that in the ideal sense, that would be the case."

Finally, a document provided by the proponents was a 1999 review in the British Journal of Hematology where Dr. Lockhorst concluded, "It is difficult to draw definite conclusions from these studies. It seems premature to conclude that intensive therapy is the standard approach," which, indeed, the proponents told us every chance they got.

Those are the major reasons why I dissented from the conclusions of the panel which are in material provided to you. I don't think I have to go into the panel recommendations and answers to the HCFA questions.

I would ask Leslie Francis and Dr. Bergthold to comment further on format and process issues that they saw as problematic for our panel.

DR. FRANCIS: I want to underline, of course, the points about not having an analysis of the materials before the meeting and, also, the balance of time not having anywhere near what I thought was an adequate amount of time to discuss the quality of the evidence with respect to the questions that were put to the panel.

I might also just add to what Dr. Holohan said for this discussion that I thought that there were really significant issues about how the questions were framed. I will just note that the judgments about what endpoints we were looking for of this panel were different from the judgment of the other panel that we have just discussed.

Our vote on the third question was that appropriate measures of successful outcomes included overall survival and quality-of-life measures. But, in fact, we had also talked about questions like whether or not complete or partial response, and we rejected those. So there is a difference right there, I think, between the panels.

DR. BROOK: It is treatment, though.

DR. FRANCIS: It is true; it is treatment. And that might make a difference. But whether it is reasonable and necessary is the standard. It seems to me it is an open question for all of us.

Also, there was some possibility to discuss but we never really got to talk about whether or not differences among tumor types mattered with respect to the quality of the evidence. I will call to your attention that the minutes, themselves, and this is a process question--when I got this packet, it was the first time I had seen the minutes.

There is at least one respect in which my recollection of the minutes and Linda's do not jibe with what we thought happened. That is the second question. "Regarding the second question, the panel was

unanimously in favor of the motion that age should not be a limiting factor. However," and this is a quote from the minutes, "the panel was reluctant to determine which groups of patients should be eligible and directed HCFA to consider whether or not patients with resistant relapse should be included in establishing its coverage decisions."

Our memory was that the panel had thought there was not enough evidence to support any kind of coverage and had wanted to make that recommendation for patients with resistant relapse. And that simply goes to the question of--I mean, I would raise that as a process question about how we should review and use the minutes.

But I am mentioning it here because I think one of the flaws in the panel process was that we didn't have an opportunity, in a clear way, to look at different types of diseases. It shows up here in this specific example about the minutes.

DR. SOX: Sharon wants to reply, I guess, to that last point about the minutes.

MS. LAPPALAINEN: The minutes of the meeting are based on the transcript. They are not based on recollection. We use the transcript to guide us on the minutes.

DR. BERGTHOLD: I did, too. I thought she made the motion specifically--

MS. LAPPALAINEN: Does someone have the transcripts for those--

DR. BROOK: Let me just get st clear. Two of whatever the number of panelists believe that the motion that they agreed to is exactly opposite to the one that is said here?

DR. FRANCIS: The one that is said here is that the panel directed HCFA to consider whether or not patients with resistant relapse--I at least understood the vote to be about--on that particular point, that they were specifically excluded from any kind of a positive recommendation.

DR. BERGTHOLD: I did, too. I just also wanted to make the point that I thought that it was--it was the first panel and we were all feeling our way along, and I couldn't vote. But I could watch. And I took very, very good notes, myself, not realizing there was going to be such an extensive transcript. The next time, I won't take the time to do that.

But I thought that the panelists did not address the issues of evidence adequately. I was surprised by the vote, that it went the way it did in terms of approving this. I attributed some of this to some of the consumer speakers, public speakers, an 85- or 88-year-old man who runs 15 miles a day and is alive because he had this treatment, were very compelling and persuasive to some of the panelists.

So, just as sort of a process suggestion, I think that we need to sort of figure out a way to prepare our panelists to focus on the evidence and try to sort of look at anecdotal issues as anecdotal issues.

Someone mentioned that this morning, that you may very well want this for your own family. My father-in-law died of multiple myeloma and I had a personal interest in it.

But I think I still would have, had I voted, voted that there wasn't sufficient evidence to apply this across the board to the Medicare population.

DR. SOX: One question that I wanted to ask and follow up with a comment of my own was the issue of applicability to the Medicare population. What kind of discussion did you have about the applicability of the findings which were all in patients under 65 to the Medicare population?

DR. FRANCIS: Very, very little, if any.

DR. SOX: With my own permission, I would like to--the major randomized trial presented outcome data for all patients and then for patients under age 60. So it was a relatively easy task to subtract the patients under 60 for each time point from the total number of patients to come up with a survival curve for patients between ages 60 and 65.

That was the easy part. The hard part was doing the statistics on it and I didn't have enough confidence in my statistics, so I don't have those there.

[Slide.]

Here are the findings. For the patients who were under age 60 who got the stem-cell transplant, these are the figures at 35, 45 and 60 months, and for the group who got conventional therapy, under age 60, here are the figures with, apparently, a plateauing for the younger group who got high-dose chemotherapy.

For the people who were over age 40, this is the line that describes the group of patients who got high-dose chemotherapy--

DR. FRANCIS: Do you mean 40 or 60?

DR. SOX: I'm sorry; this line here corresponds to patients who are between 60 and 65 who got high-dose chemotherapy and stem-cell transplant. And this is the figure that applies to the patients between 60 and 65 who got conventional chemotherapy.

So, basically, there remains a pretty substantial survival advantage for patients at 45 months who are between 60 and 65 but by 60 months, almost everybody is dead.

So that concludes my brief analysis. It seems to indicate a trend toward less effectiveness in older people but, clearly, that is all you can really conclude from it.

The floor is open for panel comments on this particular issue. Who would like to start?

DR. ALFORD-SMITH: I guess the only comment I have at this point is I am probably a little more confused than ever. Quite simply, I guess it goes back again to what we have been essentially discussing all day and that is it is a process issue. So I am somewhat unclear at this point that the committee chair, the panel chair and vice-chair, are you coming with direct opposition to what the overall panel recommendations were?

That is part of my question. And then the other part is then what is the role of the chair as they guide, hopefully, their panel in some way. It appears to me as if that is somewhat unclear.

DR. SOX: That latter question is not a disinterested question coming from a chair of a panel.

DR. ALFORD-SMITH: Absolutely.

DR. SOX: So if I could ask the three representatives from the committee to comment on the first question about whether you basically were in agreement or disagreement with the panel's ultimate vote.

DR. HOLOHAN: From my point of view, I think that is on the record. I wrote a dissenting opinion which you have been given which I think explains why I dissented. The handouts that I gave you were provided to all the panel members prior to the meeting. It was an attempt I made to focus on the evidence.

I think my introductory statement to the panel again emphasized that, in my view, we were here, and in the panel charter, we were here to look at evidence. Unfortunately, for any number of reasons, I do not believe that happened. I think part of it was the time allotted for the panel members to actually debate and discuss evidence was inadequate.

I think there was a reluctance, perhaps out of misplaced politeness, to ask the hard questions of some of the proponents, not necessarily patients or patient advocates who testified but the proponents. And I think, from my point of view, there was, in a number of instances, an apparent lack of interest in the data for reasons that I cannot explain.

Since this was the first panel meeting, as it became clearer to me what was occurring, I tried to avoid, perhaps too much, being highly directive which I saw could be a very negative attribute of the panel chair particularly considering the fact that I didn't have a vote.

If you do that in that circumstance, then you run the risk of being accused of having railroaded a panel into a conclusion that they, in fact, didn't believe. For their own reasons, the panel reviewed, listened to the evidence, I presume read all the papers, and came to a conclusion that I, personally, thought was logically and scientifically not defensible.

DR. SOX: Leslie, do you want to speak for yourself?

DR. FRANCIS: Yes. I guess I need to say I voted for the panel recommendations but with a great deal of reluctance because it seemed to me at the moment that I actually cast that vote that it was the best of a number of bad choices.

The first of the bad choices was simply a function of the fact that there was not enough time to get as good a hold on the evidence as I wanted. The second really had to do with how the questions were framed because this is a therapy where the issue is survival. So it is big stakes. So it is something that, in my sense about evidence, I was prepared to go with a little bit less rigor given the high stakes.

However, the data looked much better for one tumor type than for other tumor types and there wasn't a way to disaggregate that in the vote that we had to cast nor was there a way to try to see whether any of that correlated with age. If we had been able to do that, I think we would have--I mean, I can't speak for other panel members; I can just give you a descriptive account of my own thinking and my own vote. Maybe that is enough.

DR. GARBER: I just really have a question. I have been thinking over the evidence that was presented and so on, and it occurred to me that there is a fundamental question that we still haven't answered and I, too, am asking as an interested party viewing my upcoming panel meeting.

Suppose we had the right study--that is, a randomized controlled trial in the relevant patient population. What would we have asked the panel to consider as evidence of necessary and reasonable, that it be no worse than conventional therapy, chemotherapy, or that it provide a statistically significant improvement over conventional chemotherapy.

I got the feeling from the discussion implicitly what we have been thinking is it needs to have a statistically significant improvement. One can make arguments either way, but I would like to see us going from panel to panel using similar criteria. Conventional chemotherapy, if it is viewed as the sort of standard practice, is it good enough to say you are no worse or do you have to say that you are significantly better?

DR. HOLOHAN: I would submit that, given the fact that this is riskier to the patient, it is incumbent, in my view, on the clinician to be certain that, given the higher risks, the benefits are greater.

DR. FRANCIS: It also mattered a lot that cost was off the table on that because when you looked at the data, there were more differences for response than there were for event-free survival and how do you think about things like three months more in the way of event-free survival when there are higher risks and immensely higher costs?

DR. DAVIS: I would like to revisit Alan's question but in a hypothetical where the risks are the same between the chemotherapy we are looking at and the chemotherapy that is in standard practice already. I

am not an oncologist and I don't deal with chemotherapy, but I would imagine that it would be helpful to have two equivalent chemotherapies if they are equally efficacious and both covered by insurance, given that some patients, I would think, might not tolerate one particular kind of chemotherapy and, therefore, might be a candidate for an equivalent kind of chemo in terms of efficacy and toxicity risk.

DR. HOLOHAN: That, in fact, is the case and is common in oncologic practice. But I am not sure what you are getting at. Are you talking about whether I would choose cytoxan, methotrexate and 5-fluorouracil or cytoxan, adriamycin and 5-FU for--

DR. DAVIS: I am really just getting at Alan's question, do we have to show statistically significant enhanced efficacy or simply equivalent efficacy.

Wasn't that your question, Alan?

DR. GARBER: It is an absolutely fundamental question.

DR. HOLOHAN: Where the risks are identical, as far as we know.

DR. DAVIS: Yes.

DR. GARBER: See, Tom, one of the problems is that if you do the properly designed study, it takes toxicity and risk into account. If you had a well-powered study and you showed equal survival curves, that is already embedded in the study design. What I would contend is that almost any rational process can avoid this question of cost or inconvenience.

It is utterly insane, by most people's standards in other settings, other nations, to say that a treatment that costs many times as much money only needs to be equal in efficacy. Now, I realize there is some question about whether we can consider cost. But this would be a very odd system, indeed, if we said that you don't need to be any better, you only need to show you are no worse even if it costs ten times as much money.

Let me add, by the way--we have heard from industry people. This isn't so much an industry question. It affects industry, but if affects everyone. I think about medical procedures; how many physician hours are involved. High-dose chemotherapy has costs that involve all kinds of things. It is not the drug, primarily. Some of it is the peripheral stem cells and some of it is the hospital days. There are a lot of things involved.

One question that we will have to grapple with is if we ignore costs--well, ignore costs or not, is our standard equal efficacy or is the standard "must be superior?" If we can't resolve that, it is very hard to see how, when we go back to our individual panels, we will be able to give them guidance about how to make determinations.

DR. SOX: It seems to me you are making a very strong case that we have to take cost into account. Otherwise, we may find ourselves in an absurd situation such as the one you described where something costs ten times as much and has equal efficacy. But I guess the question is do we make a general rule, or do we leave it up to each panel to decide but call attention to issue and provide them with some of our own thinking about how to approach that issue.

DR. DAVIS: But the other question is if cost is the same, do you just need to show similar efficacy or greater efficacy? Antibiotics might be a good example where, it seems to me, if the cost is the same, you would like to have one more antibiotic with the same indications in case resistance is found in some patients.

DR. SOX: We have to solve this problem, but not right now.

DR. HILL: Thank you.

DR. SOX: Other comments?

DR. BROOK: If you go back to the HMO literature, the problems that they have gotten into trouble with, when they have had one person get one therapy and another not gotten it, that is when they get sued because of the inconsistency and the variation, one doctor advocating something and somebody not.

I think it would be a mistake if our process would not include uniform guidance across--it may vary because of the diagnostic versus therapeutic, but the principles ought to be uniform across the panels. I believe our technical advice for HCFA ought to be for that uniformity.

I believe that some of these issues we are going to have to address. For instance, I don't believe adding equivalent therapies to the marketplace does anything other than make a chaotic system worse. The report from the National Academy of Science on the error rate of medicine is partly a function of that; if you have more options, you screw up more times because you don't know what you are doing.

That is my personal belief. My technical advice to HCFA would be, based on having done research in the quality-of-care literature, it is more things that are literally equivalent which will produce mistakes because we don't have a system for managing them today.

But that is my belief. The question is how are we going to put together a set of technical processes here that really push this wheel forward within this process that HCFA can run. I think all of these questions we have to answer, in terms of what is going on. Otherwise, we are going to get this inconsistency from panel to panel.

The question about cell type, Leslie, I remember the original conversation with HCFA about coverage was, "You can't do that," because they want to know whether they should pay for this procedure in multiple myeloma patients. If I remember, the ICD9 doesn't get code "cell type" into the ICD9.

If they are limited by that, then we are going to have to suggest to HCFA that they change their carrier reporting ICD9 codes to include those prognostic things that would make a procedure useful or not.

The analogous argument would be carotid endarterectomy is a very useful procedure in some very few people when it is done by the right person. It is not a useful procedure for anyone that has a little bit of plaque in their vessel. So are we going to also provide technical advice to HCFA that this whole process requires them to rethink the way claims data and coding goes to both the carriers and up so that we can distinguish prognostically important differences among patients that are coded the same way on the ICD9 code.

MS. RICHNER: Welcome to the industry world.

DR. BROOK: I have been there. The question is are we going to really--because all of these things, up to now, if you look at--let me just put one other issue on the table. If you compare the U.S. to every other country in the world, developed country, we literally use less hospital days than anybody else including the U.K. We have less physician visits.

So where is all this money going? It is not going, according to the industry, into profit. It is going into technology and into very expensive--and so the question here is, as we do this and think about this in the global pattern of what is the production of health, I think we are going to be cognizant of these bigger and broader issues.

MS. RICHNER: Once again, it is a process issue here. I am at a loss. I am going back to, probably, Daisy's original question, how can we make a decision. Once again, I didn't even have this material until a few hours ago, this last packet, but without having some kind of consistent process for the panels to decide, my recommendation--I don't have a vote, but it would that this, once again, would go back to the panel after you clarify what the questions really should have been in the first place to ask.

DR. EDDY: At this point, I am just emphasizing points that have already been made so I will be brief. It is inconceivable to me that we don't have a standard set of--that we don't develop and get a standard set of definitions, criteria, principles and so forth. I cannot imagine how it would serve HCFA, the public, the industry or anyone if every panel or every individual on every panel did things as he or she happened to see it.

So we simply have to do that. There are lots of different issues that we have to tackle. Just a list that has come out today is whatever definition exists of reasonable and necessary, I would like to see it, as ambiguous as it might be, anything important about the legal and legislative context.

The commitment to evidence; are we really committed to evidence? Is that the bottom line or is that just one thing that we take into account along with testimony of patients, testimony of experts, society opinions and things like that, questions about levels of evidence, cost. Do we take it into account at all?

If so, how? You can imagine a lot of subcases there.

The role of biological outcomes versus health outcomes, which we touched on a little bit; that has to be resolved. How we use indirect evidence and put together chains of evidence, the role of modeling, the role of evidence reviews, the appropriate comparisons to make, the best alternatives, no-treatment, placebo, and so forth; the issue that Alan just raised, whether we are asking whether the treatment in question is no worse than, equal to, or better than, and so forth and so on and how we address that depends upon how we are taking into account costs.

So all of this has to be worked out, I think. I am tempted to give my personal opinion about every one of those things but I won't because that is clearly not what we are doing here. I just feel compelled to have some sense that we will have a process for getting these things worked out extremely quickly, I would say, if at all possible, before the next panel meeting because every panel meeting that is held between now and the time we have worked these things out is in jeopardy.

We will be back here, once again, talking about how that particular panel may or may not have come to the right conclusion. So either HCFA has to do it and hand it to us. Or HCFA does it, hands us a draft, we comment on it, they redo it. Or HCFA can ask us to do it. Or HCFA can farm it out.

At this point, I don't particularly care. I just think it is absolutely essential that, somehow, it be done extremely quickly.

I also have a lot of comments about the process. I will wait. Let me just tell you what I would like to comment on. The common features of the two panels that have been held were that they didn't have enough time to do their job. Everyone kind of feels dissatisfied about that.

There are groups that have been doing this for a while. I am thinking of the Blue Cross/Blue Shield Tech Program. I see Sue Gleason here in the audience. She is now with HCFA working on the coverage process. She started the Tech Program sixteen years ago, I think, something like that. It works.

I was tempted to walk through how the tech process would handle each one of these things. In the tech process, we assess, probably discuss, ten to fifteen technologies in a day feeling quite happy that we have had a complete discussion of the evidence. It has to do with all these other things, all these other aspects of the process being set up. The criteria are there. The definitions are there. The workup is done. The questions are very carefully thought out ahead of time.

The evidence is analyzed specifically for each particular question. The staff makes a recommendation. Then the discussion occurs. And, in a half an hour, we can go over an awful lot of material. Then the thing is rewritten. It is reviewed and so forth and so on.

Industry knows what they are going to see. They see the criteria. They know what is going to be applied. For the complex issues, there are forums that are held, and so forth and so on. You don't have to accept

that model, but the point is there are ways, I think, of getting around this problem that we have seen in the last two panels, if we pay very careful attention to the process.

DR. HILL: I know I am in the presence of scientists when we ask them a question and we get a whole bunch of very good questions back. We hear you. This is very helpful.

In keeping with trying to articulate the standards by which we are making decisions, I would ask you to think about how you are going to treat the panel's findings that you are going to be voting on whether to ratify and pass on later on today. This refers to both of the two panels that were before you today.

I think that is critical, how do you treat those findings and recommendations. We had hoped that you would not treat them as a situation where they have to make the case to you, they have to prove their assertions past your skepticism. We have not anticipated, or thought of this, as a de novo hearing. We have a record that is not a tabula rasa.

We had hoped that you would give some weight to the panel's recommendations. Now, how much weight, maybe you want to talk about, but at least to the level of calling it a rebuttal of presumption, maybe even substantial, something that has to be overcome for good reason rather than the paradigm being you are treating it as something that they have to argue to you to prove to you.

I don't know if you all agree with that, but that is the preconception that we had hoped the panel's recommendations would come to you with.

DR. BROOK: Can I ask a question about that? I agree with that. I don't think we should be refereeing again. But what we have heard is something very different from what I expected to hear. We are refereeing a process that nobody knew what the game was, or the game was not specified adequately or prepared.

I think, in general, you are right. I don't know how to handle these two meetings in a constructive way because we want to make it constructive. But what we have heard from both panels, as David eloquently or forcefully just described, is a set of process problems that may have resulted in us saying that we should be uncomfortable with what we heard in terms of the conclusions, not because of the content of the conclusions but, regardless of which way those conclusions came out, that the process just was not sufficient to produce any conclusions at all at this moment.

The first panel's conclusions are much less definitive, about they changed the questions, the first that was discussed. They changed the questions. There doesn't seem to be any coverage implications at all hardly in them. The second panel is a little bit more definitive.

But I am wondering would you reflect on that, in the general agreement about what our role is, that we are not going to re-referee this process but what we have heard is that we ought to do something about the process.

That comes back to the Chairman's role. The Chairman's role ought to be to have a checklist to make sure, if that is David's checklist, that once we agree on the process, to make sure that everyone on the panel is aware of the process, they understand it and that they are following.

Then, if they conclude, however they conclude, they at least have--the Chairman has made sure that the process, as the Executive Committee has sort of outlined, has been fulfilled.

DR. EDDY: Hugh, in trying to address your question, I was thinking very much along the same lines as Bob. I don't think that our role can be to review the decision that they made, in a sense, to act as a second jury because we weren't there. And the whole point of the initial panel meeting was to allow the panelists an opportunity to hear from the public, hear from the proponents, hear from the opponents, and things like that.

And they will have spent a day and a half or two days at it. So we can't possibly reproduce that. For us to sort of rethink the same issues and just place ourselves on top of them, I think, would go a long way toward undoing the very thing you want to accomplish with the whole panel process.

So what is our role? I think our role is to do what we have just been doing which is review the process. Do we think that the process that we intend to have followed--by we, I mean a "W" there, we being HCFA--that you want to have processed was processed.

The test question I have in my mind is do I get the sense that the panelists feel that they had an adequate opportunity to really come to a well-reasoned conclusion. That is about all I have got to go on right now. The sense I get is certainly "no" for the second panel, and I got a big question mark on the first panel. I don't quite know, so I would probably abstain on that question at this point.

But I think that that is a question that we, on the Executive Committee, can ask ourselves. I think that is an appropriate role for us--that is to review the process--but if we agree with the process, but disagree with the conclusions, I would say we should not overturn the conclusion, as much as I might disagree with that, because to do so would undo the very process that you are trying to create.

DR. BROOK: I think that should be a vote or a recommendation or whatever we do, that our job is not to ratify, overturn or act as the second jury on the content, but, rather, it is to make sure, by talking to the chairs and the representatives that the process that was followed met the process that we specified.

Now, we are in a "Catch 22," since, for these two panels, we specified no process, we are asking them to have read our minds about what we would have hoped before they actually met. So that puts us in a very ticklish position about what to do today.

DR. SOX: But a conclusion we could draw without aiming fault at anybody was that these panels met prematurely before we had provided them, and HCFA had provided them, with an adequate framework

and support for making a decision that was close to the evidence and that it would be better to try again when we have got that process in place.

DR. EDDY: May I just make one more point which I think is very important. If we did do that, it would not, in any way, be a statement that the panelists got the wrong answer or did wrong or weren't smart or didn't try or weren't motivated or anything like that.

It is simply a question about the process and whether the process served the needs that HCFA had when it convened the panel.

DR. SOX: We are going to have to move on now to a period of public comment unless there are any other comments that simply can't wait. At the end of the period of public comment, I will ask Sharon to frame up exactly what we are voting on and we will vote, and then we will adjourn.

DR. DAVIS: After the public comment, we are just voting; is that it? No more discussion?

DR. SOX: I think we can take into account what we heard during the public comment period and anything else we want to talk about, but we will have to vote by 4 o'clock.

DR. DAVIS: I just heard a whisper here that I think is important to mention in light of the comment that David made and that is that the charge, as Hugh read, I think, earlier today was to review and ratify; is that right? So I think David was saying we might ratify the process but not the conclusion if they follow the process.

So maybe we need to have some more discussion about that, maybe not now, but later.

DR. SOX: We have fifteen minutes for public comment. We have five scheduled commentators. You will each have three minutes. Because the time is late and I want to spend it mostly on discussion and the vote, I will cut you off at the end of your three minutes.

Maybe I could just ask, is Dr. Nagourney here? Dr. Weisenthal? I know you are here. Dr. Kiesner, are you here? Dr. Kern, are you here? Dr. Panke? So we have four people, so it is four minutes each.

Dr. Nagourney, would you like to start, please.

Open Public Comments

DR. NAGOURNEY: I am Dr. Robert Nagourney. I am a hematologist, oncologist. I should start off by saying that I have absolutely no idea what the spread on cost between chemotherapies and charges is, and the chemotherapies that I administer are all done through a hospital. I don't get any money for giving them so I would like to clarify that I have absolutely no vested interest in what gets given to anyone.

I am also the founder of Rational Therapeutics, which is a cancer center. I have paid my own way here. I have no affiliation with anyone else. I was going to show slides, but with four minutes, it is ridiculous. So I would, instead, make the point, one point that I think came up repeatedly from my experience at the meeting that I attended, which was the November 15 and 16 meeting.

I am an investigator in an area of study that is based on cell-death events, apoptosis, programmed cell death, that which constitutes the modern understanding of cancer biology.

One of the reasons that we, today, do not believe more fully in the results of these studies has been because I believe they have been based on the wrong scientific endpoint and study, the study of cancer as a disease of cell proliferation and growth, and we have not focussed on the cancer as a disease of cell death or the perturbations in cell-death events now known as apoptotic research.

What I was going to show you, had I had the chance to show you the slides, was one that I took artistically in the last couple of days. It was a picture of apples and oranges. The reason I wanted to show that is because, in essence, the reason that your committee members from the November 15 and 16 committee could not come to a conclusion was because it was such a widely varied collection of technologies, endpoints, measures, results.

My great concern, from everything I have heard and everything I heard at that meeting, was that the data that was repeatedly presented could be distilled to possibly one, two or three studies. The single best study that was presented, and the only one that conferred evidence of significant survival advantage over a long period of time with a large number of patients studied, was a study done by Andrew Bosenquet published in the British Journal of Hematology where chronic lymphocytic leukemia patients had a survival that was demonstrably better if they were sensitive to fludarabine.

There was a study alluded to by Dr. Sausville regarding small-cell cancer of the lung which has a survival advantage and a cell-death endpoint, the same endpoint, the same conceptual background that supported Dr. Bosenquet's study. I presented a small study in breast cancer, again based on cell-death measures, apoptotic studies, that correlated quite strongly with outcome in terms of survival, a small study in breast cancer.

These do not meet Dr. Burke's very stringent criteria but what they do is distinguish two very different areas of investigation, that based on cell death, apoptosis, programmed cell death and how that discriminates sensitive and resistant patients and the remaining older studies and iterations thereof which were based on cell proliferation.

Without making that distinction, I think it becomes utterly impossible for the data to be analyzed, for the survival advantages to be found. I think that it is a further reinforcement of the comments made earlier that this was a complex collection of sophisticated measures that could not possibly be lumped together.

I am very fearful, as someone who is deeply involved in this area of investigation, that this committee

will make a blanket decision, an umbrella determination, and leave me as an investigator what I consider to be the modern area of investigation tethered by this procrustean bed of one type of study and "I must fit into that."

That is a death knell for development. I would also make the point that to approve this at this time, when so many good studies will be forthcoming through GOG and other investigative groups, will enable people to charge for a service whether it is good or bad and I think, personally, will put an end to good investigational work.

We have seen it in breast cancer. In the high-dose therapies in breast cancer, if you pay for it, they will do it. I feel that we have many examples in the past where things that are widely used, lidocaine in acute myocardial infarction, corticosteroids in sepsis, there are lots of times that people do things that may not be good.

Thank you.

DR. SOX: Thank you very much, sir.

Dr. Weisenthal?

DR. WEISENTHAL: There is no time whatsoever to present data or to debate with anybody. What I would like to do instead is to just--and my nice, five-minute presentation, I am not going to be able to make in view of what I have just heard.

So, what I would like to do instead is to just comment on this process. It would be a real travesty were this committee here to overturn the findings of the Technology Assessment Committees. The chairmen in those committees were not even allowed to vote and yet the chairmen here are misrepresenting the findings of their own committees, grossly misrepresenting them.

I know that if the panel members of the committee that attended our meeting would be here that they would not agree with the way that it has been characterized. Now, I want to just read to you from the transcript because this is quite important. Dr. Ferguson, at the meeting, asked the question, should we be voting on whether it should be covered or not.

Somebody alluded to the fact that it was kind of an ambiguous recommendation. That is because they were instructed not to vote on should this be covered, unlike the multiple myeloma meeting. In the multiple myeloma meeting, the committee was permitted to vote on the coverage decision.

But, here is the wording. Dr. Ferguson said, "For us to add some more questions like, 'Should Medicare cover this, yes or no,' for or panel, or 'Under what circumstances for our panel,' I do not think was our job. Has that been changed?"

Dr. Bagley: "No; we spent a lot of time with questions with staff. We spent a great deal of time toiling over them," et cetera, et cetera. So he is basically saying, "You shouldn't be voting on it. You should be restricting yourselves to those questions we ask."

But here is what he said, and this is quite important. He says, "So I think that we are particularly interested and the number-one goal should be, as you know, to go through these questions and give us not only answers--and they aren't really yes or no questions, necessarily--but to give us some discussion and to give us some rationale. That is one of the biggest reasons for having this transcribed word for word so that discussions around these questions can--and we can use this as guidance in helping to develop the policy."

The record is here. It has been transcribed word for word. If you go through this record--if you go through this record, I challenge anybody to say that the strong consensus of the committee was that these technologies should be covered. Read the words that are there. Do what Dr. Bagley said you should do.

I will just give you one example. A member on the committee here, Dr. Murray, what he said. "So those are my concerns. Having said that, I also felt that in some of the studies that were presented, I was impressed with some of the leukemic studies and some others, that there is some usefulness and it needs to be mined. But it needs to be mined carefully and under the right conditions."

Oh, no; pardon me. That is Dr. Ferguson. That is not the one I wanted to read. I was going to make another point with that.

Here is Dr. Murray. "The third point is just my own reaction. Spending my life generally in the laboratory, I have tried to analogize all of the situations, the questions, to existing laboratory tests. There is no question the many laboratory tests which are routinely approved currently have nowhere near the evidence, nowhere near the accuracy and predictive value that these tests that we are considering today, that we heard about yesterday, have already demonstrated.

"Yes; we do have to look at outcomes. We have to look at outcomes measured in different ways. We have to look at evidence. But the evidence--even if the bar is raised higher, the evidence that we have heard certainly exceeds the evidence that we have for many, many tests currently in use."

Finally, if you go through, person-by-person, read the transcript, read what they are telling you, they are telling you that they should be covered. The last panelist to talk, before we concluded, was Dr. Mintz. Here is what he said.

He said, "My concerns have already been stated by others, but I want to use this opportunity to state that I think that the sense of the committee was best expressed in Motion No. 3 and that these tests show promise for clinical utility and that the motion deliberately did not state--distinguish between sensitivity and resistance testing.

"So I think the sense of the committee reflects that it is supportive of both sets of testing. I would only add that I only hope that I only hope that coverage is adequate to permit this technology to be used."

That is what the committee felt. There is on doubt from reading the transcript. That is what should be focused upon. And for you, here, just to reopen the whole issue based on misrepresentation by the committee chairmen who were not allowed to vote on this for a reason, I think is a travesty.

There were many misrepresentations made, such as the lack of survival data. I showed a slide at the meeting. There are fifteen studies showing strong correlations with survival. This is not just based on response. I am an oncologist and I know the importance of survival.

DR. SOX: Your time is up.

Dr. Kiesner?

DR. KIESNER: I am Frank Kiesner. I am President of Oncotech. Obviously, that makes me an interested party. This is a very difficult issue and it is very confusing for us who sit outside and listen to the dialogue. Our expectation was that a process was in place and that our participation in the process would yield a valuable result which would be helpful to the HCFA staff.

With that as an overview, I would like to make two points. First, I don't want you to accept as an axiom what Dr. Nagourney said. I would refer to what Dr. Eddy mentioned. In other words, the arguing of the science, the determination of one technology versus another, that is appropriate in the setting that was provided by the panel.

We brought in physicians from around the country which would give, and who did give, a different viewpoint and a very important viewpoint.

The second thing is what I have heard today is that you are focussing on the process. I think that that is very important and it is needed because there has to be a structure if we are going to have confidence in the result. However, I would feel troubled if the panel would equate evidence with good policy.

Evidence is a key ingredient in good policy but the wonderful process that HCFA has worked so hard to put together should not just be isolated to evidence. What I saw in the wondering meeting conducted by Dr. Ferguson and Dr. Murray and all of the other participants was something far beyond evidence. It was judgment.

It was judgment based on independence. It was judgment based on broad knowledge within their area of expertise and then diverse expertise. I think that is a key ingredient that we must find a way to bring that judgment to the assistance of the HCFA staff.

I view MCAC as being a true guardian of the rights of patients and I view that the emphasis on evidence

supports that. But don't leave out the fact that these people brought judgment that otherwise wouldn't be present. I think judgment leads to good policy.

Finally, I would caution that a change--in other words, a nonratification based on policy questions or the fact that we learned we need more time to deal with this, or we have to define the questions that the panel deals with more narrowly, I would feel badly if the process and what we learned would, in any way, impinge or be pejorative to the technologies that were discussed.

So be careful about the message that would be sent out in the event that there is a nonratification.

Thank you very much.

DR. SOX: Thank you, sir.

Our last speaker is Elizabeth Panke.

DR. PANKE: My name is Elizabeth Panke. I have no financial interest with any of the companies or individuals involved in tumor assay studies. I also personally assume all the costs of coming to this meeting.

I am a pathologist practicing in Cincinnati, Ohio. I received my Ph.D. degree from the University of Southern California in experimental pathology. I received my M.D. degree from the University of Cincinnati and I finished my pathology residency also at the University of Cincinnati.

Currently, I am a Director of Genetica Laboratories in Cincinnati, Ohio. My husband, who is also here, is also a pathologist and he is a medical director of six hospital laboratories in Cincinnati, Ohio.

The way we are familiar with tumor assay studies is because we have been sending and using these services for our patients in our hospitals. Unfortunately, I am also familiar with these studies because I had to personally use them. In July of 1999, I was diagnosed with ovarian cancer, stage IIIA. Immediately, I was placed on standard ovarian chemotherapy of carboplatin and taxol.

Within weeks, it was evident my tumor was growing very fast with this chemotherapy. I developed ascites, evidence on CAT scan that my tumor was spreading throughout the abdomen and my C125 was rising.

I was changed to topotecan. Again, the tumor was very rapidly growing through topotecan and, at this point, I was producing over 2 liters of malignant ascites every five days.

We had decided to go ahead and use the tumor assay studies at this point. We had decided to send my malignant cells that I was producing in my abdomen to two companies. We chose Oncotech and Rational Therapeutics. The reason we chose these two companies is because they use two different

methodologies.

We had no idea if we would get the same results or different results. However, time was of the essence. Let us look at the results that were produced by these two companies. Let's look at Oncotech. He is distributing these results.

When you look at the results produced by Oncotech, we can see that the results give us an impression that my tumor is not resistant to most of the drugs that were tested. In fact, the only drug that appears to have extreme drug resistance is taxotere on the second page.

We can also look at the drugs which showed the least resistance in the study which are carboplatin, taxol and topotecan. These are the very drugs that I had failed. Obviously, you can get these results and there is very little option for treatment.

The cells collected for these two studies both from Oncotech and Rational Therapeutics were collected five days apart and there was no intervening treatment.

Let's look at the results produced by Rational Therapeutics. The results produced by Rational Therapeutics, on the other hand, show that my tumor is resistant to most of the drugs being tested. Additionally, this report also indicates what drugs or drug combinations my tumor is sensitive to.

At this point, it looks like my tumor was sensitive to cisplatin and gemcitabine. On November 11, I received my first treatment. Within two weeks, my ascites was completely resolved and my C125 dropped by two thirds.

In summary, I believe that there is a difference between the results produced by tumor assays which is the cell proliferation as the endpoint and by tumor assay studies that use cell death as an endpoint. I also believe that additional studies and guidelines are needed for technology. I propose that a recommendation for a broad-based coverage of tumor assay systems be not made until the result of further assays and further studies are in place.

DR. SOX: Thank you.

Recommendation and Vote

Now, we have about twenty-five minutes for discussion and voting. Ron, do you want to pick up where you left off with respect to process?

DR. DAVIS: I just scribbled out a motion. It is mainly for the sake of discussion, which I think may reflect some of the comments that are made so far. So here is how it would read: that the Executive Committee, one, take no action on the panel recommendations at this point; two, thank the panels for their conscientious work to date; and, three, ask the panels to reconsider these matters after the

Executive Committee and HCFA establish a consistent process for panel review and assessment of the evidence.

DR. SOX: That needs a second before we can discuss it.

DR. EDDY: Second.

DR. SOX: I hear a motion and a second. Now it is time for discussion. Sharon seems to be trying to get my attention here.

MS. LAPPALAINEN: I would like to read a few things to the committee before they begin their voting and recommendation process. You have kind of gotten a little ahead of me.

At this time, Dr. Sox will call for a motion and he will be asking the voting members of the panel to vote on the reports of the MCAC specialty panels. I have already named the members of the panel who are voting committee members to the record so I need not do that again.

HCFA would like the committee to either ratify, with no other modifications, or ratify upon condition--for example, resolutions of clearly identified deficiencies which have been cited by you or by the HCFA staff. Examples of deficiencies could include the resolutions of questions concerning some of the data or changes that you would like to see implemented.

If you believe that modifications are necessary, then, in your recommendations, you should address the following points: the reason or purpose for the modification and the information that is required to be submitted. Obviously, if the panel should choose not to ratify either of the reports, HCFA would like to have your reasons why they are not being ratified and what conditions would need to be stated in order for the Executive Committee to put them into ratification or ratification with modification.

Once the Executive Committee makes a formal recommendation to us, we will post it on our home page. Within 60 calendar days of receiving the recommendation, we will either adopt to MCAC recommendation or adopt it with modifications, or we will notify the requester and the public why we disagree with the MCAC recommendation.

If we choose not to adopt the recommendation, our notification will explain the reasons why we have decided not to adopt the MCAC recommendation and we will also notify and identify further evidence that we require to be submitted to us. Again, we will post our decision on the home page.

Thank you.

DR. SOX: Thank you. We have a motion on the floor which basically is to take no action, to thank them for their efforts and suggest that they take up these questions again after we have a process in place that everybody is satisfied with. Is that the sense of the motion?

DR. DAVIS: Correct.

DR. SOX: So it is now open for discussion both with respect to the merits of the motion but also how the motion might be crafted in a way that would respond to the charge that Sharon gave me before I prematurely opened the discussion.

Alan?

DR. GARBER: I agree with much of sense of the motion except I am not sure, and am uncomfortable, to lump both of the panel recommendations together in one motion in this way although I understand the rationale--i.e., that a process wasn't in place. I, frankly, feel that the two situations are different.

I would potentially vote--I am not sure whether I would vote different ways on both of them, but there is one where I don't think that, unless there is different evidence, that I could, in good faith, go along with the panel's recommendation. It is partly a recommendation that they may have reached because they didn't have a process in place, but I cannot, in good faith, vote to send something back to the panel if I thought I would have trouble endorsing the same recommendation if they made it after they adhere to the procedures because we have the same evidence in front of us aside from the public testimony part.

MS. LAPPALAINEN: Dr. Davis, do you accept the amendment to split the motion into either the lab panel or the drug panel?

DR. DAVIS: That would be fine.

DR. SOX: Just a comment on your last point. It is true that all we have is this big, fat binder with undifferentiated information in it. Presumably, if it came back through a proper process, it would be organized in a way that, at least possibly, might change our mind.

DR. DAVIS: Just to pick up on that point. Let's just say, hypothetically, that we took action to not ratify a panel recommendation and then HCFA went along with that and then, three months, six months, down the road, we developed this process that we all agree with, I think that earlier decision of nonratification could be challenged based on not having followed a process that we subsequently developed.

MS. LAPPALAINEN: Let me be clear on that point. HCFA cannot take action on what the medical specialty panels did. We can only take action when the Executive Committee transmits what the medical specialty panels did to us.

DR. DAVIS: That doesn't change the point I made. I am saying if we actually take action today, as Alan was suggesting we could, and that action is challenged legally or in whatever way, it could be challenged on a procedural issue if it doesn't follow a process that we develop a few months later.

DR. SOX: Sharon, do you want to comment?

MS. LAPPALAINEN: No.

DR. FERGUSON: I have a question, Ron--

DR. SOX: John, Hugh would like to respond to that point, so then I will turn to you.

DR. HILL: Very briefly, we hope to be refining and improving the process continuously so that if we say that it is challengeable because we don't follow a subsequently developed process, we are out of the box all the way through.

DR. SOX: Thanks for waiting, John.

DR. FERGUSON: I just wanted to clarify your motion, Dr. Davis. Did you mean that not ratifying today but that the same information would be brought to the Laboratory and Diagnostics Panel and Dr. Holohan's panel to go through the whole thing again under the new process? Is that what you were suggesting?

DR. DAVIS: Right; along with any new information that becomes available, but also recognizing that if it is done the way the Blue Cross/Blue Shield process works, it might not take a day and a half. Maybe, it could be done in two or three hours.

DR. FERGUSON: So, in other words, revisiting it with the new procedures in place.

DR. DAVIS: I am not suggesting that you have another day-and-a-half meeting going over the same thing. Don't get me wrong. Maybe it could be a two-hour revisit and then you would move on to the next several items that HCFA would like to be on that panel's agenda, at the same meeting.

DR. MURRAY: With regard to the Laboratory and Diagnostics Panel, the motion pertaining to the Laboratory and Diagnostics Panel, ratification of their actions, I am prepared to vote in favor of that because I believe that, while the process was flawed, the motions that were passed were sufficiently general to be, for lack of a better word, innocuous.

I know that HCFA expected the panel to come up with specific recommendations. Having difficulty with that charge, we changed the wording to be relatively noncommittal. Yes; we did find evidence to support the utility. We couldn't swallow the word "benefit." We changed it to "utility."

My recommendation, my feeling is, and I can't put a motion on the floor because there is already one on the floor, but my recommendation would be that, with regard to the Laboratory and Diagnostic Services Panel actions that Sharon's second option, which I don't think I can phrase exactly, but that the actions

be ratified but sent back to the committee for clarification, and the clarification would be in the form of the specific questions that have been alluded to on a number of occasions.

I don't think that can be done in two hours. I am afraid that it will another day-and-a-half meeting because the questions will have to be method by method. Our failing on the first attempt was we threw everything into the same basket and then made general statements; "Yes, someplace in that basket, there is utility." I think we have to take the items out one by one and address them individually.

DR. SOX: Other comments? Let's focus, now, on the motion to deal with the tumor sensitivity testing since we have agreed to split them. So let's continue the discussion of that and we will come to a vote.

Other people wish to comment?

DR. BROOK: My reading of this is that we don't want the first product of a committee to be innocuous. This is too expensive. If the chairs and we believe that what we have produced is sort of like what the NIH once did saying that women who have appropriate indications should be offered a vaginal delivery after a C-section, and then you spend your next year trying to figure out what are appropriate indications and why you had to spend three days coming up with that recommendation.

I don't really want innocuous recommendations. I would like to see if the process can be specific enough, clinically, so that it takes care of both evidence and opinion in a way that produces a set of recommendations that may be more than innocuous, that may be really constructive, at the end of this.

This is a matter of life and death. It potentially could help the field if we were more specific. I thank you for going to be, I think, ethical on this or--not ethical; what word am I looking for? Responsible. I think we ought to make sure that HCFA, if we pass this motion, actually can move this process fast enough so that both of these technologies get a proper hearing quickly since these are both life-and-death technologies and get a quick hearing and get some much more specific recommendations and answers to some specific questions about this.

AUDIENCE: Mr. Chairman, may I make a comment?

DR. SOX: The open session is closed. I am afraid I will have to deny your request, with respect.

DR. MAVES: I just want to comment, again, on process. I realize the conundrum that Sharon and the staff at HCFA finds itself in as much as they have a process and a schedule and a time line that they need to and should adhere to. On the other hand, I am sympathetic to the motion because I do think that we have a time schedule and sort of requirements from HCFA but, in a way, we have been left with a little bit of a void here--more than a little bit of a void--on the process.

We have heard much comment about that today. Looking back on another experience I had a number of years ago when the Resource Base Relative Value Scale Update Committee was initially put together,

we had a similar process where, for the first couple of meetings, people had to kind of walk through kind of a mine field of problems. But that worked out over a period of time and the process has been ironed out fairly concretely.

I think we are at that same juncture here. I, personally, don't feel uncomfortable with the tentative nature that we have had on these deliberations because I think we are all feeling our way along this. I think, rather than do an injustice to the panel members of the proponents of these two technologies, I think the motion helps us move the process down the line, but it doesn't, necessarily, close off any opportunities for anyone at this point.

Until, I think, we get a better process put in place, that may be the best we are going to be able to do with this piece of information. At least, it might be the best I can do with it.

DR. FRANCIS: I would like, if we don't act today, to have a sense of it be that, to be publicly understood, that what we are doing is neither ratifying nor not-ratifying but merely delaying a decision about ratification. To that end, I have actually been looking at the schedule here. We have another meeting of the Executive Committee on the 1st and 2nd of March.

The next meeting of the Drugs, Biologics and Therapeutics Panel is the 2nd and 3rd of March. And the next meeting of the Laboratory and Diagnostics one is the 26th and 27th of April. Then we could do a ratification decision on the 6th and 7th of June.

I don't know if it is a friendly way of understanding your motion to say that, in a way, what we are doing is tabling a decision about--in effect, what I would like to see us thought of as doing is tabling a decision about ratification pending--remember, these two panels met before there was any meeting of the Executive Committee at all, pending further and better advice to the particular panels and a request to the panels if they want to say more at those meetings to us with this guidance.

I don't know if that muddies the water or not, but that is how I would hope we would be understood.

MS. LAPPALAINEN: The committee is voting at this point so we may not able to--we cannot recognize the non-voting members. That was done during the open committee deliberation time.

DR. DAVIS: Just in response to Leslie's point, my motion, I think, is very consistent with what you were looking for in your comment. That is why I chose the wording, "Take no action," which, I think, is equivalent to tabling. Thanking the panels was in recognition of the fact that it was not their fault that they didn't have a structure in place when they met.

DR. FERGUSON: But the third part is to revisit it again; in other words, convene the panel again over the same issues.

DR. DAVIS: Correct.

DR. FERGUSON: I must say that, just speaking personally, I am not sure that that would change our panel's view. I think, Bob, I am echoing what you said, am I not? Do you think that, by revisiting, it will change things much? I, personally, don't.

DR. MURRAY: I think that if it were revisited with the instruction to, or with the direction to, view each of the various tests on an item-by-item basis, yes; it probably would change.

DR. BROOK: Don't you think this needs to be revisited--I mean, aren't we supposed to give advice regarding coverage?

DR. MURRAY: Yes.

DR. BROOK: I don't understand what the process, in this case, was different from the process in the other case. Wouldn't you have to go through and segregate--have a process which takes apart all these tests, puts them into some grouping that make clinical sense, then provide the evidence, then get the testimony in a public process, and then, basically, make an up-and-down decision about coverage.

Or is that too specific for what the process--and would that change--

DR. FERGUSON: My understanding was, at least on our committee, that we were not supposed to say, "yes, cover this; no, don't cover it," but we were supposed to evaluate the evidence for supporting it or not supporting it.

DR. MURRAY: We looked at a number of different procedures. Somewhere, in those procedures one used for different tumor types, we did find some utility. That doesn't really help HCFA because now it is in their lap to go back and say which ones get covered and which ones don't get covered.

So I think it will be a very difficult issue but, I think, if approached systematically and with a sound structure, that it can be done. In some cases, we are going to find there is simply not enough evidence. But, for some, I think that we will find that there is enough evidence.

DR. BROOK: Then, why on this other panel--I am confused now. On this other panel, regarding the sixth question, the panel voted unanimously in favor the motion that Medicare should not consider treatment--coverage." On the seventh question: "The panel voted unanimously in favor of the motion that coverage should not be related to the source of the cells."

Those are coverage questions, if I look at the language there. You were told that you couldn't answer those questions? That, even more, argues to me that we ought to go back and ratify this motion for both of these.

DR. SOX: It is five minutes to 4:00. It is time for us to take a vote. We are going to vote on the two

issues separately. If you could restate the motion, putting it in the context, first of all, of the tumor sensitivity testing issue.

DR. DAVIS: That the Executive Committee: one, take no action on the panel recommendations at this point; two, thank the panel for its conscientious work to date; and, three, ask the panel to reconsider this matter after the Executive Committee and HCFA establish a consistent process for panel review and assessment of the evidence.

DR. SOX: Any last comments before we vote?

DR. EDDY: Just a question. If this is voted down, then we turn around and have a vote on ratification? Is that correct?

DR. SOX: Yes. That's right. And, if it is not, it will be taken by HCFA as no ratification for the record, I guess; is that correct?

DR. HILL: That's correct.

MS. LAPPALAINEN: You need to ask for a second to the motion.

DR. SOX: I think we had a second earlier. Let's just do it to be sure. Somebody second it, please.

DR. EDDY: Second.

DR. SOX: All in favor, please raise your hand.

[Show of hands.]

MS. LAPPALAINEN: We have eight in favor.

DR. SOX: All those opposed.

[Show of hands.]

MS. LAPPALAINEN: We have four opposed. Would those opposed please state why they are opposed?

DR. FERGUSON: I think I did in my discussion. I am not convinced that revisiting--I don't have problems with tabling it or thanking our committee for our hard work. I think that that is fine. I will accept that. I think that it is not necessary to revisit it under the way you have suggested in the motion.

DR. MURRAY: My opposition is, basically, because, as I stated before, I would prefer to see ratification

and then sending it back for much greater specificity.

DR. JOHNSON: As part of the process on review and ratify, I think the panel did the best they could with what they had and with the recommendations they had. I think it was either vote up or down on the ratification, so I would like to see it ratified.

DR. PAPATHEOFANIS: What Dr. Ferguson said is pretty much what I would have said.

DR. SOX: That motion passes 8 to 4.

Ron, do you want to restate the motion but now in the context of the myeloma question.

DR. DAVIS: The wording would be identical. Do you want me to reread it?

DR. SOX: Yes, please.

DR. DAVIS: That the Executive Committee: one, take no action on the panel recommendations at this point; two, thank the panel for its conscientious work to date; and, three, ask the panel to reconsider this matter after the Executive Committee and HCFA establish a consistent process for panel review and assessment of the evidence.

DR. SOX: All in favor of the motion, please raise their hand. This is the same motion but applied to myeloma. DR. EDDY: Second.

DR. SOX: We have a second. All in favor, please raise your hand.

[Show of hands.]

MS. LAPPALAINEN: We have nine for.

DR. SOX: All those opposed.

[Show of hands.]

MS. LAPPALAINEN: We have three in opposition. If you could please state your reasons.

DR. FERGUSON: I did actually attend the myeloma and my reasons for voting against would be very similar to my reasons for voting against the one for our panel.

DR. JOHNSON: Same reason as prior.

DR. GARBER: I also agree that I don't think sending it back to the panel will change my conclusion about it unless there is no evidence, as I stated before.

DR. SOX: We have acted and, in so doing, we have put a great deal of pressure on ourselves to come up with a process that will work. As the chair, I assure the panel members and the public that I am going to work very hard to make this happen and I know I will be joined by my colleagues.

Are there any last comments before we adjourn?

DR. EDDY: This is a question. Some of the groups, at least the diagnostic imaging group, will be meeting before the next meeting of this Executive Committee. So my question is whether we want to postpone those meetings until we have a formal process worked out lest we be sitting here reviewing the same kind of situation.

DR. SOX: I know what Sharon is going to say.

MS. LAPPALAINEN: No; we cannot postpone because a Federal Register notice is being printed, which we are required to do at least 30 days prior to a meeting, which gives the public time to put in comments regarding it.

DR. SOX: Meanwhile, the chair of that committee will have been present at this discussion and can try to lead the committee in a way that will minimize the problems.

MS. RICHNER: Am I allowed to ask one question?

MS. LAPPALAINEN: We are finished with voting, so, yes.

MS. RICHNER: How will you handle the process that is being written by HCFA now in terms of how that is going to reflect the process that you all are going to design? How is that going to be integrated?

DR. HILL: We will have to see what it is, how it comes out, before we can answer that question.

MS. RICHNER: How what comes out?

DR. HILL: The process that HCFA is writing.

MS. RICHNER: When will that be published?

DR. HILL: We don't know.

MS. RICHNER: Because now it is not open to the public so how would we have privy to that?

MS. LAPPALAINEN: You will have privy to it when the subcommittee transmits it to the Executive Committee.

MS. RICHNER: No, no; I am talking about the HCFA criteria reg. That is pretty critical, I think, to how we design our process.

DR. SOX: Sharon has a few housekeeping comments, at least I think they are. And then I will make one wrap-up comment and then we are doing.

MS. LAPPALAINEN: Just the conclude today's panel meeting, I would like to remind you that the tentative schedule for the MCAC is available as a handout at this meeting, or you may wish to call the HCFA Advisory Committee information line. It is a new telephone line that has all of our advisory committees here at HCFA so that the public, who may not have computers, may have access.

The toll-free line is 1-877-449-5659. That is a toll-free number. Or, for local calls, you can call 1-410-786-9379 and specify the Medicare Coverage Advisory Committee. Again, we do have a web page which is available.

DR. SOX: I would like to thank the members of the panel, the members of the public who turned out for this session, especially those who attended at their own expense to try to enlighten the committee. I now declare us adjourned.

MR. KIESNER: May I make one short comment?

DR. SOX: Yes.

DR. KIESNER: Dr. Whyte alluded to Alfred Tennyson this morning about the slow-moving science. I would like to remind everyone, he also wrote The Charge of the Light Brigade. As an entrepreneur trying to get reimbursement, the line, "Cannons on the right of me, cannons on the left of me, cannons in front of me," came to mind. I think he put those two poems together.

MS. LAPPALAINEN: Thank you.

[Whereupon, at 4:05 p.m., the meeting was adjourned.]